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Research Article

**OPTIMIZATION AND CHARACTERIZATION OF
MICROEMULSION FOR NASAL DRUG DELIVERY****Rathod Sayali P*, Jadhao U.T., Ghogare Jyoti . D, Panchal Pranita P.**Department of Pharmaceutics, SVP college of pharmacy (B.pharmacy) ,Hatta Tq.Basmat,
Dist-Hingoli**Article Received: September 2022 Accepted: September 2022 Published: September 2022****Abstract:**

The present study was aimed to develop and evaluate micro emulsion of Ibuprofen for intranasal delivery. Micro emulsion formed by Capmul PG8, tween 80, propylene glycol is clear, transparent and stable. Among various formulations formulated ME-1, ME-2, ME-3, ME-4, ME-5, ME-6 were clear, transparent and stable. Globule size of final optimized formulation ME-5 had a diameter of 155.4 nm and width of 36.65 nm; this confirms the Isotropic nature of micro emulsion In vitro diffusion study was also done on bovine nasal mucosa. the release of the drug from the formulation showed a lag time of 30 min. 42.11% of drug was released Micro emulsion showed higher drug release which may be due to solubility enhancing of surfactant and co-surfactant. The microemulsion systems are transparent and stable at ambient conditions for 1 month. Stability study was carried out at 40°C & 75% RH for one month. Formulation was stable for total period of study.

Keywords- Microemulsion, Capmul, Nasal drug delivery, surfactant.

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INTRODUCTION:

The treatment of central nervous system (CNS) disorders is challenging because of a variety of formidable obstacles for effective and persistent delivery of drugs. Even though the drugs used for the treatment of CNS disorders are potent, their clinical failure is often not due to lack of drug efficacy but mainly due to shortcomings in the drug delivery approach. However, potent the drug may be, but if it cannot cross the blood brain barrier and reach the CNS in order to elicit its pharmacological action, it is ineffective. Hence, scientists are exploring the novel approaches so that delivery of the drugs can be enhanced and/or restricted to the brain and CNS⁽¹⁾.

Intranasal administration offers a practical, non-invasive, alternative route of administration for drug delivery to the brain. Intranasal administration allows transport of drugs to the brain circumventing BBB, thus providing a unique feature and better option to target drugs to the brain. There is a need to design a delivery system that can provide rapid transport of drugs across nasal mucosa and longer residence time in the nasal cavity^(2,3). Microemulsions have been explored widely as a delivery system to enhance transport of a wide range of drug molecules. The addition of a mucoadhesive agent such as bioadhesive polymer helps in retention of the formulation in the nasal cavity.⁽⁴⁻⁵⁾

Microemulsion is a thermodynamically stable, isotropically clear product that has a droplet size $<0.15\mu\text{m}$. It consists of oil phase, surfactant, co-surfactant and aqueous phase. O/W micro emulsions represent a promising prospect for the development of formulations suitable for the incorporation of poorly water-soluble drugs due to high solubilisation capacity, as well as the potential for enhanced absorption. In addition, the solution-like feature of microemulsion could provide advantages such as spreadability, dose uniformity and formulation physical stability.⁽⁶⁻⁸⁾

MATERIALS AND METHODS:**Materials-**

Ibuprofen was provided by Research laboratories Ltd, Mumbai., India as a gift sample Capmul PG8 as a gift sample from Abitech labs Ltd, Mumbai India. All other chemicals and reagents used were of desired analytical grade.

Methods-**Drug-Excipient Compatibility Studies by FT-IR****Analysis**

Infrared spectrum of any compound or drug gives information about the groups present in that particular compound. The IR absorption spectra of the pure drug and physical admixtures of drug with various excipients were taken in the range of $4000-400\text{ cm}^{-1}$ using KBr disc method and observed for characteristic peaks of drug⁻⁽⁹⁻¹⁰⁾

Drug-Excipient compatibility was carried out by FT-IR analysis. Initially the IR spectrums of pure drug, Ibuprofen, Capmul PG 8, Tween-80, propylene glycol were obtained. After that admixtures of drug with other excipients were prepared and IR Spectra was obtained. The obtained spectra of physical admixtures was observed for major peaks and recorded. The results of this observation were concluded that there is no interaction between the drug (Ibuprofen) and other excipients (Capmul PG 8, tween-80, propylene glycol).

Selection of components

The components of the ME system were selected on the basis of miscibility of the drug and the HLB value of the component emulsifier

Selection of Oils

To find out the suitable oil, which can be used as oil phase in microemulsion, and provide excellent nasal permeation rate of Ibuprofen. The solubility of Ibuprofen in various oils including castor oil, isopropyl myristate, Capmul MCM, olive oil, Capmul PG8 was measured at 25°C .

Selection of surfactants and co-surfactants:

The non-ionic surfactants do not ionize at any great extent in the solution, they are greatly compatible with both anionic and cationic substances; various nonionic surfactants like, Tween-80, Tween 20, co-surfactants like, PEG-400, propylene glycol, were subjected to titration. Finally, Tween-80 and propylene glycol were selected as an ideal surfactant and co-surfactant for the system.⁽¹¹⁾

Microemulsion formulation and phase diagram study

A hypothetical pseudo-ternary phase diagram of an oil/water/surfactant/co-surfactant system (two corners of the diagram represent 100%(w/w) of the particular component (oil and water) and the third corner represents a 100% (w/w) of a binary mixture of surfactant and co-surfactant (SCoS), including the dilution lines for investigation of: (a) the SCoS

efficiency to solubilize the equal masses of oil and water (SCoS_{min}) (the dashed line) and (b) the water solubilization capacity of a surfactant/co-surfactant/oil mixture at constant SCoS/oil weight ratio 1:1 (W_{max}) (the full line). At insufficient percentages of SCoS as well as at water concentrations higher than W_{max} , two phase systems (2Φ) are observed; for SCoS concentrations above SCoS_{min} and at water concentration slower than W_{max} , there is a single phase region (1Φ); at very high SCoS concentrations liquid crystals (LC) are formed.⁽¹²⁾

Water titration method and phase diagram construction

The pseudo-ternary phase diagrams were constructed using water titration method to obtain the components and their concentration ranges that can result in large existence area of microemulsion. Capmul PG8 with Tween 80 (non-ionic surfactant) as surfactant and Propylene glycol as co-surfactant were used as components in the phase diagram construction. For each phase diagram construction, desired concentration of surfactant and co-surfactant (S/CoS) at certain weight ratios were prepared. Nine transparent and

homogenous mixtures of oil (Capmul PG8): Smix (Tween80/ Propylene glycol) at 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 w/w ratio were prepared by mixing with magnetic stirrer. Each mixture was then titrated with water and visually observed for the phase clarity and flow ability. Three such phase diagrams for S/CoS at 1:1, 2:1, 3:1, 4:1 were prepared.

Formulation of Microemulsion

Selection of formulation was done on the bases of stability of the selected microemulsion ratio of Tween 80: PG (1:1) and observation for clarity, transparency. As our objective was to get less viscous formulation with minimum possible use of surfactants, then final selection of formulation is by comparing the viscosity of all formulations, the formulation which gave less viscous formulation having minimum use of surfactant was selected as final optimized batch. The concentration of the drug that should be present / ml of the ME so that therapeutic level is achieved. Ibuprofen has nasal dose of 2.86mg. Hence 2.86mg of dose must be present in 500 μ l of formulation for single dose administration in each nostril. Maximum 15% of oil in formulation can solubilize 2.86mg dose per 500 μ l of formulation.

Table No 1: Composition of the selected Microemulsion ratio

Formulation	Capmul PG8 %v/v	Smix(Tween 80:PG)(1:1)	Water%v/v	Ibuprofen (mg)
ME 1	5	40	55	2.86
ME 2	5	45	50	2.86
ME 3	10	40	50	2.86
ME 4	10	45	45	2.86
ME 5	15	40	45	2.86
ME 6	15	45	40	2.86

Evaluation

Optical Transparency

Optical transparency of the formulation was determined by inspecting the sample in clear and transparent container under the presence of good light against reflection into the eyes, and viewed against black and white illuminated background.⁽¹³⁾

pH determination

The pH of the formulation was determined by using the digital pH meter. pH fundamentally represents the value of hydrogen ion activity in solutions. The pH meter was calibrated with the help of the standard buffer preparation of pH 4 and pH 7. Measurement of pH was done in the triplicate to reduce the margin of error.⁽¹⁴⁾

Conductivity determination

Conductometry is a useful tool to assess microemulsion structure. It has been previously demonstrated that a consistent correlation does exist between structure type and microemulsion electroconductive behaviour⁸⁵. The conductivity of the formulations was measured on the conductivity Meter calibrated with the KCL solution. Each measurement was taken as triplicate to reduce the margin of error⁽¹⁵⁾

Viscosity determination

The rheological properties of the microemulsion system depend upon the globule size, emulsifiers and co-emulsifier and its concentration, phase volume ratio etc. The viscosity of the ME solution presented an important parameter in the evaluation of the system as it can affect the stability of the preparation. Hence the viscosity of the ME system was determined at the different points of the stability studies. Many microemulsion show changes in the flow properties as function of the time⁽¹⁶⁻¹⁷⁾

All the measurement were carried out using the Brookfield viscometer. The ME solution was filled in the beaker. Spindle no 61 is attached to the viscometer. Null Zero point is adjusted by rotating the base screws. Then spindle is dipped in the beaker up to the mark and rotated at different gear speed according to set gear. All the readings were taken in triplicate and taken the average of all readings at different gear speed for a particular sample.

Globule size determination

Globule size is an important parameter for, microemulsion evaluation. Globule size effect the stability of formulation. Globule size can be determined by light scattering. Globule size of final selected batch was determined. Dimensions of microemulsion globules were measured by Malvern zetasizer by using disposable cuvette at 25°C.

Refractive index

The Abbey Refractometer measure the range of refractive indices for those Pharmacopeial materials for which such values are given. Other Refractometer of equal or greater accuracy may be employed. To achieve the theoretical accuracy of ± 0.0001 , it is necessary to calibrate the instrument against a standard provided by the manufacturer and to check frequently the temperature control and cleanliness of the instrument by determining the

refractive index of distilled water, which is 1.3330 at 20°C and 1.3325 at 25°C. As transparency is one of the characteristic of the ME system, it can also be used as the evaluation parameter of the ME solution. Refractive Index (RI) changes with the transparency of the solution, this parameter may be used to determine opacity that may occur due to the phase inversion, if any, or any interaction that may occur between the compositions of the system. Any change in the RI of the system may indicate the stability problem of the system. All the measurements were done on the Abbey's Refractometer. The apparatus was calibrated with the liquid of known RI like Cyclohexane⁽¹⁸⁾

In-vitro drug diffusion study

Diffusion kinetics was carried out using Bovine nasal mucosa in phosphate buffer (pH 6.8) for a period of 3 hr using Franz-Diffusion cell. Tissue samples were inserted in Franz diffusion cells displaying a diffusion area of 3.14 cm². Seventeen millimeters of phosphate buffer saline (PBS) pH 6.8 at 37°C was added to the acceptor chamber. The temperature within the chambers was maintained at 37°C. After a pre-incubation time of 20 minutes, 2 ml of Ibuprofen Microemulsion was placed in the donor chamber. At predetermined time points, 1 ml sample were withdrawn from the acceptor compartment, replacing the sampled volume with PBS pH 6.8 after each sampling, for a period of 3 hours. The samples withdrawn were diluted with buffer solution, filtered and used for analysis. The amount of diffused drug was determined using a UV-visible spectrophotometer at 265 nm (Linearity range = 2µg/ml to 12µg/ml, $r^2 = 0.989$).⁽¹⁹⁾

Stability study.

Stability studies were carried out on the dosage form i.e. micro emulsion of this formulation was stored at $40 \pm 20^\circ\text{C}$ and $75 \pm 5\%$ RH for duration of one month. After one month the formulation were evaluated for parameters like viscosity, pH, conductivity, Refractive Index etc.⁽²⁰⁾

RESULT & DISCUSSION:

Interaction studies were carried out to a certain any interaction of the drug with the excipient used in the preparation of Intranasal Drug Delivery Systems. From the IR spectra it is observed that there were no changes in the main peaks in IR spectra of pure drug, drug and polymer, which shows there were no physical interactions due to some bands formation between drug, solvent and polymer. The major spectra of Ibuprofen were observed at 2985, 2900,

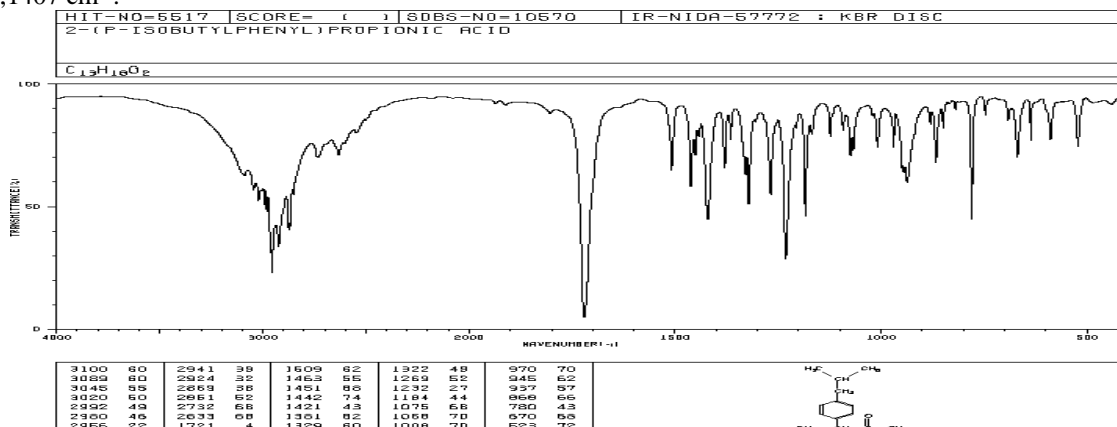
1687,1407 cm^{-1} .

Fig1: IR spectra of Ibuprofen

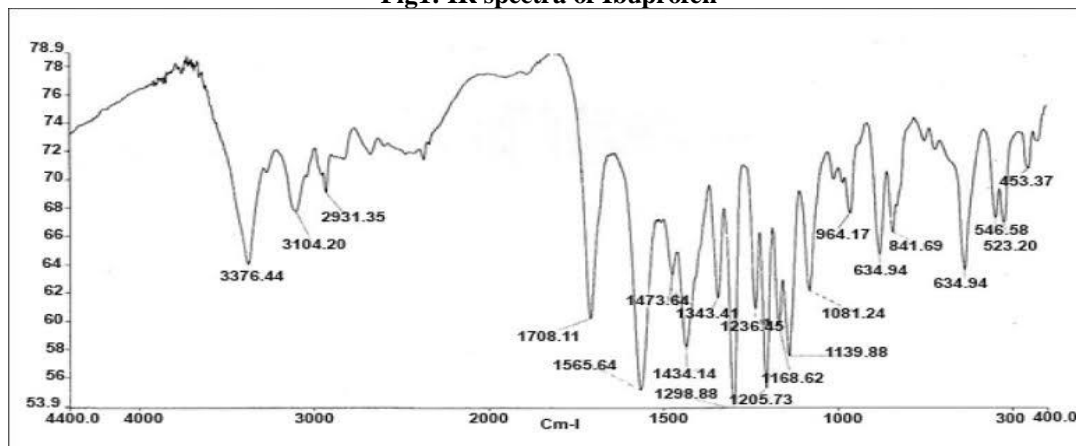


Fig 2: Compatibility of Ibuprofen with Excipients

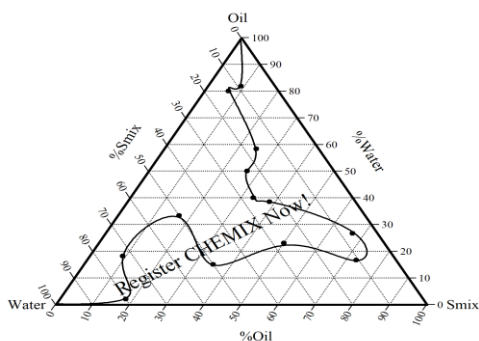
There are no extra peaks seen other than the normal peak in the spectra of the mixture of the drug and excipients and so there is no interaction with the drug and excipient and they are compatible with each other. The IR spectra of the drug and polymer combination were compared with the spectra of the pure drug and individual excipients in which no shifting of peaks was significantly found, indicating the stability of the drug during microemulsion formulation development.

Selection of components

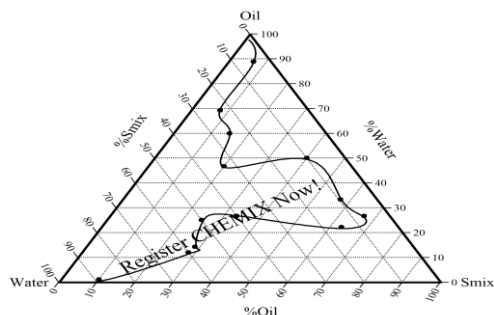
Selection of the oil was on the basis of solubility of drug, Capmul PG8 was chosen as oil. Solubility of Drug in Capmul PG8 reported to be 326.40 ± 0.15 mg/ml. Polyoxyethylene sorbitan mono-Oleate (Tween 80) was chosen as the surfactant. HLB (hydrophilic lipophilic balance) value of Tween 80 reported to be 15. Selection of co-surfactant was on the basis of solubility with drug and titration method. Propylene glycol was chosen as co-surfactant. Finally, Tween-80 and propylene glycol were selected as an ideal surfactant and co-surfactant for the system.

Study of pseudo-ternary phase diagram

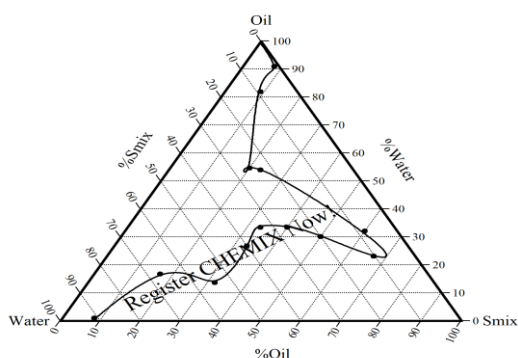
Ternary diagram-tween 80&PG(1:1)



Ternary diagram-tween 80&PG(2:1)



Ternary diagram-tween 80&PG(3:1)



Ternary diagram-tween 80&PG(4:1)

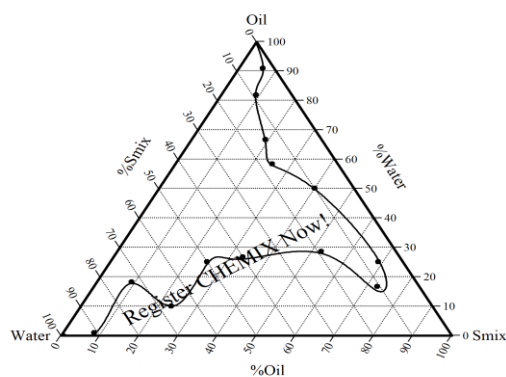


Fig 3: pseudo-ternary phase diagram of Tween 80 : PG

From these pseudo- ternary phase diagrams the microemulsion region were identified on the basis of their stability and it was found that within each ME region the solution of the ME was transparent and with low viscosity. No distinct conversion from oil in water to water in oil ME was seen. The rest of the region in the t-phase diagram shows either turbid solution of microemulsion or the gel form of the mixture.

The effect of changing concentration of surfactant (Tween 80) to co-surfactant (Propylene glycol) in the ratio of (1:1, 2:1, 3:1,4:1) was studied by using Capmul PG8 as oil phase. Pseudo-Ternary Phase Diagrams were drawn for various ratio of surfactant to co-surfactant. Phase diagram study shows that as the concentration of surfactant goes on increasing; the microemulsion region as well as water emulsification also increases. Microemulsion region was least for the

1:1 ratio of surfactant (Tween 80) to co-surfactant (PG). Water solubilization capacity increased with increased concentration of surfactant. This increase in microemulsion area may be due to change in HLB value of Smix, As such surfactant and co-surfactant possesses high and low HLB value respectively. But the mixture of these components makes a suitable HLB value. As the concentration of co-surfactant in the Smix increase, it will decrease the HLB value to very low. Surfactant (Tween 80) to co-surfactant (PG) ratio of 1:1 showed maximum water solubilization and stability. Hence emulsifier: co-emulsifier ratio was fixed at 1:1.

Evaluation of Microemulsions

From the optical transparency it was found that all the formulations were clear, transparent and stable All the formulations have pH in the range **5.29-5.77**. Hence all the formulations were considered as

the compatible with the nasal secretion of pH 6.5. All the formulations were found to have stable pH during their storage at room temperature. The conductivity of the formulations was found to have the negative value. This is due to the fact that greater solubilization of water phase by means of the emulsifiers and co-emulsifiers and thus the oil globules carrying the charge was negligible and thus gives negative charge. From the observation table it

is clear that as we move from ME-1 to ME-6, viscosity values goes on increasing. Increase in viscosity due to increase in the oil and concentration of surfactant mixture. As surfactant mixture is most viscous component in the formulation of microemulsion, increased concentration of surfactant in the formulation leads to increase in the viscosity of formulation. ME-5 formulation has viscosity of 139 cps as it consists of 40% of surfactant mixture.

Table No 2: Evaluation Parameters of the microemulsion

Formulation	Appearance	Ph	Conductivity	Viscosity (cps)	Refractive Index
ME-1	Milky	5.23	-0.2	110	1.582
ME-2	Milky	5.45	-0.3	127	1.692
ME-3	Clear	5.69	-0.2	131	1.451
ME-4	Clear	5.77	-0.3	136	1.459
ME-5	Clear	5.29	-0.3	139	1.435
ME-6	Clear	5.31	-0.2	147	1.438

Globule size determination

Globule size was determined by using Malvern zetasizer. Results of size analysis are represented in Fig: 27. Disposable cuvettes were used for size analysis. As microemulsion have globule size in the range of 10-100 nm. Results of size distribution by intensity graph showed particle diameter of 19.3 nm and width of 5.21 nm at 100% intensity. This much globule size confirm the isotropic nature of O/W microemulsion.

Results

	Diam. (nm)	% Volume	Width (nm)
Z-Average (d.nm): 29.6	Peak 1: 19.3	99.9	5.21
Pdl: 0.272	Peak 2: 341	0.1	78.9
Intercept: 0.844	Peak 3: 0.00	0.0	0.00

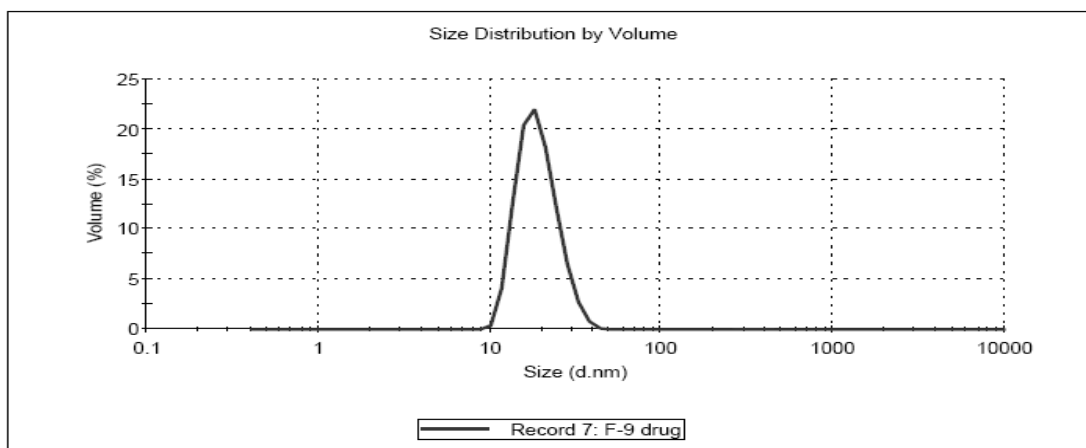


Fig 4: Globule Size distribution by intensity graph of final selected formulation ME-5

Drug diffusion study

The drug release through the bovine nasal mucosa was studied and it was found that the drug release pattern showed some lag time of about 30 min and after that it was linearly increased. Table No shows absorbance, drug concentration and the % drug release of the formulation. Formulation ME-5 was chosen for the *in-vitro* study due to its low viscosity.

Table No 3: Drug diffused from Ibuprofen

Sr No.	Time (min)	Drug diffused (µg/ml)	% Drug diffused
1.	0	0	0
2.	10	23.11	9.9
3.	20	35.6	19.4
4.	30	39.18	20.32
5.	40	50.39	25.77
6.	50	55.6	30.44
7.	60	62.56	42.11
8.	70	73.43	48.5

From the table, it is clear that, the release of the drug from the formulation showed a lag time of 30 min. and then drug release was increased, but up to 60 min only 42.11% of drug was released. This was probably due to the karatinization of the bovine nasal mucosa.

Stability Study

Stability studies were carried out on formulation containing drug for one month. After one month, the formulation were taken out and again evaluated for the parameters like viscosity, conductivity, pH, clarity etc. The results are given in the table 4.

Table No. 4: parameters studied on ME-1 optimized formulation before and after stability studies results

Sr No.	Evaluation Parameter	Before stability studies	stability study
1.	pH	5.29	5.34
2.	Conductivity	-0.3	-0.2
3.	Viscosity (cps)	153	155
4.	Refractive index	1.435	1.437

CONCLUSION:

In this study, model drug chosen for study was Ibuprofen. Tween 20 was taken as surfactant. A number of oil components have been evaluated, among all other oils, Oleic acid was selected as oil component in the formulation of microemulsion. Effect of different low HLB surfactant on water emulsification was also studied by taking oleic acid as oil phase and tween 20 as surfactant. By observing results, propylene glycol was selected as co-surfactant. After the selection of various formulation components, effect of different ratio of surfactant and co-surfactant on phase behaviour was studied. Surfactant ratio which gives maximum water

solubilisation and stability was selected. After the selection of final ratio, formulations were observed for clarity, transparency and phase separation. Clear transparent and monophasic formulations were selected and evaluated for various parameters.

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