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CHARACTERIZATION AND QUANTIFICATION OF ETHYLHEXYLGLYCERIN

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ABSTRACT: Ethylhexylglycerin is an alkyl glyceryl ether. This means that the ethyl hexyl group is bound to glycerin at one end by an ether linkage. it has been used as a common ingredient in bath products, body and hand products, cleansing products, deodorants, eye makeup, foundations, hair care products and suntan products. The compound is synthesized by esterfication of 2-Ethylhexanol and epichlorohydrin, followed by ring opening reaction of epoxy positioned at 1st and 2nd carbon in the chemical structure. It was characterized by NMR, seven - CH_2 (position 10, 11, 9, 8, 6, 4 and 2) carbons present at negative side. Tertiary carbons are present at chemical shifts 39 ppm and 70 ppm (position at 7 and 3) and primary carbons are present at chemical shifts 10 ppm and 13 ppm (position at 14 and 12). Both primary and tertiary carbons were found on the positive side of the spectrum. From FTIR studies, peak corresponding to -OH stretch is observed at 3,391 cm^{-1} and the -OH bending is seen at 1,111 cm^{-1}. By Mass characterization, the *m/z* value of the sample was found to be 204.9 (ES^-) which represents Ethylhexylglycerin. The purity and impurity profile of material was achieved by GC-FID method with >99.0%.

INTRODUCTION: The ethylhexylglycerin is chemically 3-[(2-Ethylhexyl) oxy]-1, 2-propanediol with the molecular formula and molecular weight as $C_{11}H_{24}O_3$ and 204.3 g•mol^{-1}, respectively. It is widely used as an ingredient in cosmetics and in deodorants and is commercially marketed under the brand name sensiva® SC50 [1]. It also has anti-microbial activity, therefore, is also used as a preservative [2 - 3].

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Literature review has revealed its synergistic effects with other preservatives as it boosts the efficacy of other preservatives [4 - 6]. There have been minor cases reported [7 - 10] during the period of 1990 - 2015, when evaluated at two Belgian university patch test clinics, where 13 patients were presented with allergic contact dermatitis caused by ethylhexylglycerin [11].

However, due to its several properties and rare side effects, it has been a drug of choice in many formulations [12 - 14]. There has been no literature where the drug was characterized. Therefore, the present study has been carried out to synthesize the ethylhexylglycerin using the starting materials as epichlorohydrin and 2-ethylhexanol and also to determine the physical properties of the drug

followed by characterization with the help of GC-FID, FTIR, GC/MS and NMR spectroscopic methods.

MATERIALS AND METHODS: Acetone was obtained from RANKEM, India. Cadmium trichloride of NMR grade was purchased from MERK, India. 2-ethylhexanol and epichlorohydrin of GC grade were used as starting materials for the synthesis of ethylhexylglycerine were purchased from MERCK, India.

Instrumentation: Gas chromatographic system (Agilent technologies) module 5970, waldbron Germany was equipped with an advanced flow controller (AFC), FID detector and split / split less injection unit. NMR spectroscopy belonging to the manufacturer, JEOL, model number ECS400 installed with user-friendly Delta™ software, FTIR spectroscopy and GC model number GC2025 of SHIMADZU Kyoto, Japan were used in the study for the characterization of Ethylhexylglycerine.

The column used was DB-1 having the dimensions of 30 m (L) × 0.32 mm (i.d.) × 0.25 µm (T) obtained from from J & K scientific, with Nitrogen as the carrier gas with a flow rate of 2 ml / min. The injector temperature was 280 °C and that of detector was 300 °C.

The elemental quantification CHNOS Elemental Analyzer was used. The density and Refractive index of material is measured with Rudolph Research Analytical DMDM 2911 / J457 instruments. For water content determination by Karl fisher (KF) method, Mettler Toledo KF V20 powai, Mumbai instrument was used.

Methodology:

Synthesis of Ethylhexylglycerin: Ethylhexyl-glycerin was synthesized by using the starting material as 2-ethylhexanol. It was first mixed with the catalyst and epichlorohydrin was added drop wise under cooling. This resulted in the formation of 2-Ethylhexyl glycidyl ether. The second step was a ring opening step where, the obtained product was treated with water. As a result, the layers were separated to give the crude product. It was then purified to obtain the final qualified product which was characterized. The scheme is shown below in the **Fig. 1**.

Characterization: The synthesized Ethylhexyl-glycerin was subjected to identification and characterization was carried out with GC-MS, NMR and FTIR spectroscopic methods for the confirmation of the structure. Several tests that include solubility, appearance, odour, refractive index, density, water content and presence of impurities by elemental analysis were also performed.

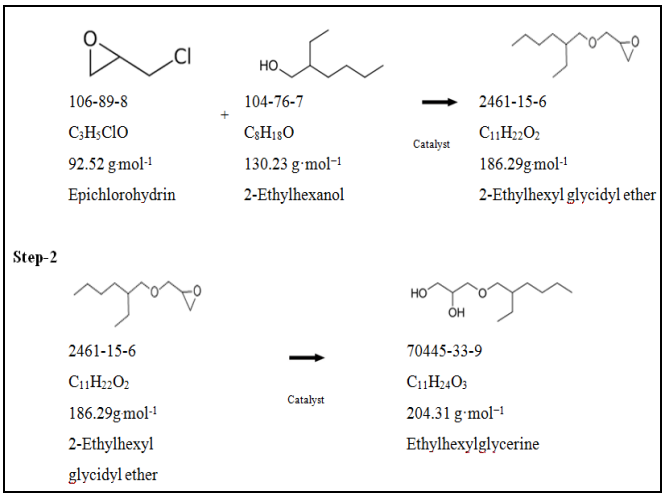

FIG. 1: SYNTHETIC REACTION SCHEME OF ETHYLHEXYLGLYCERIN

Solubility: Solubility is one of the most critical properties that have a significant impact on performance of a molecule. During this study, the sample was subjected with different solvents to determine its solubility. The solubility results were tabulated in **Table 1**.

TABLE 1: SOLUBILITY OF ETHYLHEXYL-GLYCERIN IN DIFFERENT SOLVENTS

Solvent	Solubility (g/100g of solvent)	
	Solubility %	Remarks
Water	≤0.1%	Slightly soluble
Ethanol	>50%	Readily soluble
Ethanol (10% in water)	≤0.2%	Slightly soluble
Propylene glycol	≤30%	Soluble
Propylene glycol (10% in water)	≤0.2%	Slightly soluble
Butylene glycol	<50%	Soluble
Butylene glycol (10% in water)	≤0.2%	Slightly soluble
Paraffin oil	>50%	Readily soluble
Silicon oil	≤0.01%	Insoluble
Glycerin	≤1%	Sparingly soluble

Appearance and Odour: The state of a chemical has a big impact on its exposure route and distribution behavior in various environmental compartments. Usually, the state (solid, liquid, gas)

for a chemical under normal conditions; 10 ml of the sample was taken in a 50 ml Nessler's cylinder and was placed over white surface. It was then observed transversally in diffused light for the presence of foreign matters followed by observing odour with odour strips.

Density and Refractive Index: The density and Refractive index of the material was measured with Rudolph Research Analytical DMDM 2911 / J457 instruments at 20 °C.

Water Content: Water content in the sample was determined by Karl fisher titration using methanol. Karl Fischer reagent was first standardized and then KF standardization factor was calculated using the following formula:

Factor (mg/ml) = Weight of the water taken in g × 1000 / Volume of KFR consumed

With the freshly prepared KF reagent, sample is dissolved in methanol and titrated with KF reagent. The moisture/water content is then calculated using the formula:

Water / Moisture content (%) = V × F × 100 / W × 1000

Where, V: Volume of Karl Fischer reagent consumed in the titration (ml).
F: Factor of freshly standardized Karl Fischer reagent (mg / ml).
W: Actual quantity of the sample taken (g or ml).

Boiling Point: The boiling point of Ethylhexyl-glycerin was determined in the laboratory by placing the 100 ml of sample in round bottom flask. It was then heated to observe bubbles flowing out of the tube. The contents of the tube were then allowed to cool and the temperature at which the liquid starts to flow into the tube was recorded as the boiling point.

Flash Point: Set a flash Series 3 instrument is used for closed cup. It is sealed with a lid through which the ignition source can be introduced periodically.

Elemental Analysis: Elemental analysis on carbon, hydrogen and Oxygen is the most essential, and in many cases the only investigation performed to characterize and / or to prove the elemental composition of an organic sample. Numerous compounds include no additional elements besides C, H and O, which is seldom determined separately to determine the percentage of Carbon, Hydrogen and Oxygen in the molecule. Determination of C/H/O was done using a "Vario EL III CHNSO Elemental Analyzer" by Elementar Analysen-systeme GmbH. The sample was subjected into the elemental analyzer (C, H and O). The instrument was calibrated with the analysis of standard compounds using the K-factors calculations. Thus the instrument ensures maximum reliability of the Results as the combustion gases are neither split nor diluted but directly carried to build in GC system. Simultaneous determination of CHO can be done in less than 10 min. This method finds greatest utility in finding out percentages of C, H, and O in organic compounds which are generally combustible at 1100 °C. The results are shown in the **Table 3** with its respective spectrum in **Fig. 7**.

TABLE 2: OTHER PHYSICAL PARAMETERS STUDIED FOR ETHYLHEXYLGLYCERIN

Parameters	Value
Boiling point	265°C
Density	0.9407g/ml
Refractive index at 20 °C	1.4505
Flash point	146.5 °C
Water content	<0.1%

Presence of Related Compounds: A simple, economic, and time-efficient related substance by GC-FID method has been developed for the quantification of related substances present in the ethylhexylglycerin. For this study, GC with model number GC2025 of SHIMADZU was used.

Preparation of Standard Solution: Approx. 1 g of the ethylhexylglycerin was weighted exactly and transferred in to 50 ml volumetric flask. A measured volume of 1 ml of each 2-Ethylhexanol and 2-ethylhexyl glycidyl ether was added and finally made up to mark with 50 ml of Acetone.

Preparation of Sample Concentration: 1 g of the sample was weighed accurately and dissolved in 50 ml of acetone. The samples were then injected into the GC system on a DB-1 GC column with the carrier gas nitrogen at flow rate of 2.0 ml/minute and eluents were monitored by FID (Flame ionization detector) to determine the presence of other substances (impurities) related to ethylhexyl-glycerin. The data obtained was summarized in the **Table 4**.

RESULTS AND DISCUSSIONS: Upon physical observation, the compound was found to be clear colorless liquid and from the solubility studies, the compound was found to be readily soluble in ethanol and paraffin oil with the solubility greater than 50%. In the solvents like propylene glycol and butylene glycol, the compound was sparingly soluble (less than 50%), whereas it is slightly soluble in water, 10% solutions of ethanol, propylene glycol and butylene glycol. It was found to be insoluble in silicon oil. Results of the solubility studies are shown in the **Table 1**.

Identification and Characterization: The position of the signals in a full NMR characterization of pure Saliguard EHG (Ethyl hexylglycerin) was performed as summarized in **Fig. 2 - 4**. According to the spectrum, seven $–CH_2$ (position 10, 11, 9, 8, 6, 4 and 2) carbons present at negative side of the spectrum. Tertiary carbons are present at chemical shifts 39 ppm and 70 ppm (position at 7 and 3) and primary carbons are present at chemical shifts 10 ppm and 13 ppm (position at 14 and 12). Both primary and tertiary carbons were found on the positive side of the spectrum.

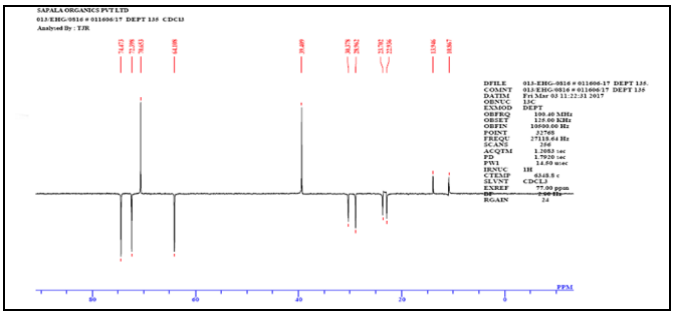

FIG. 2: TYPICAL NMR SPECTRUM OF ETHYLHEXYLGLYCERIN IN $CDCl_3$ DEPT 135

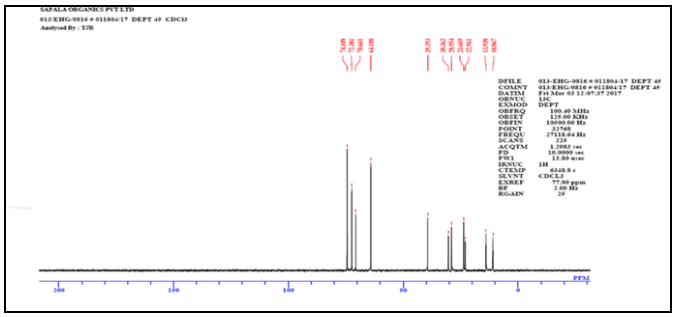

FIG. 3: TYPICAL NMR SPECTRUM OF ETHYLHEXYL GLYCERIN, REPRESENTS THE PRESENCE OF –CH, $–CH_2$ AND $–CH_3$ CARBONS ARE AT POSITIVE SIDE OF THE SPECTRUM

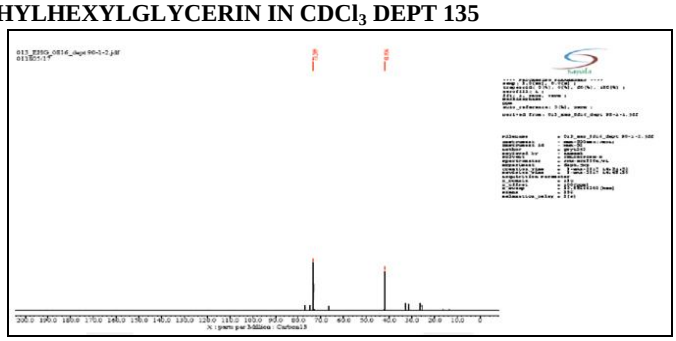

FIG. 4: TYPICAL NMR SPECTRUM OF ETHYLHEXYL GLYCERIN REPRESENTS THE TERTIARY CARBONS ON THE POSITIVE SIDE OF THE SPECTRUM

Therefore, the spectrum confirms the presence of two $-CH_3$ carbons, two -CH carbons and seven $-CH_2$ carbons present in the given sample. From FTIR studies, peak corresponding to -OH stretch is observed at 3,391 cm^{-1} and the -OH bending is seen at 1,111 cm^{-1} which is shown in **Fig. 5**. Therefore, from the NMR and FTIR spectrum, the spectral data confirms the structure of the molecule. By Mass characterization, the *m/z* value of the sample was found to be 204.9 (ESI^+) which represents Ethylhexylglycerin. The spectrum is shown in the **Fig. 5**.

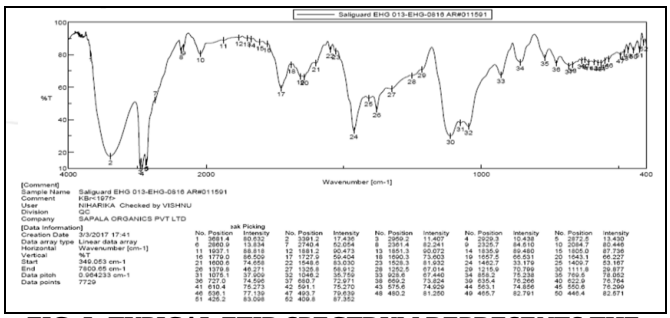

FIG. 5: TYPICAL FTIR SPECTRUM REPRESENTS THE PRESENCE OF -OH FUNCTIONAL GROUP PRESENT IN ETHYLHEXYLGLYCERIN

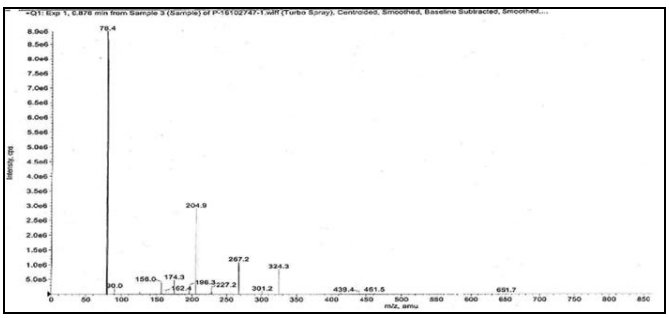

FIG. 6: TYPICAL MASS SPECTRUM OF ETHYLHEXYL GLYCERIN ELEMENTAL ANALYSIS

From the Elemental analysis results, the Ethylhexylglycerin has Carbon, Hydrogen and Oxygen elements. The % Results of these elements were exactly matching with % of each element present in molecule with respect to its Molecular formula. The following elemental data shown in the **Table 3** and **Fig. 7**, the compound confirms to be Ethylhexylglycerin.

Related Compounds Study by GC: The estimation of impurity profiles of Ethylhexyl-glycerin and related materials is always a great challenge for the efficient chromatographic separation. In addition to producing stable and volatile compounds for the gas chromatographic analysis and the selectivity in gas chromatography is determined by the structure of the stationary phase and solute factors, such as polarisability, solubility, magnitude of dipoles and hydrogen bonding behavior. The flame ionisation detector has become one of the most popular measuring devices used in GC.

TABLE 3: THE PERCENTAGE OF CARBON, HYDROGEN AND OXYGEN PRESENT IN THE SAMPLE

Element	Percentage (%)	Limit w.r.t molecular formula
Carbon	61.85%	64.7%
Hydrogen	11.35%	11.8%
Oxygen	23.55%	23.5%

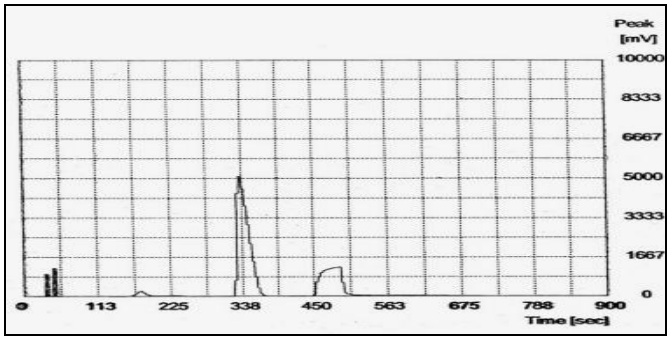

FIG. 7: TYPICAL GRAPH REPRESENTS CARBON AND HYDROGEN ELEMENTS PRESENT IN THE ETHYLHEXYLGLYCERIN

Its use is based on the measurement of variations in the ionisation current in a hydrogen-oxygen flame due to the presence of eluted substances. Chemionisation reaction occurs in the flame, assuming collision of neutral atomic excited states with molecules in their ground state. Based on the synthetic reactions involved in synthesis of Ethylhexylglycerin, identified the 2-Ethylhexanol and 2-Ethylhexyl glyceryl ether as process related impurities are present.

The Trend data of impurity profile as tabulated in the **Table 4** represents the presence of 2-Ethylhexanol is <0.02% level and 2-Ethylhexyl glyceryl ether is <0.1%. The Typical GC Chromatograph is shown in the **Fig. 8**.

TABLE 4: TREND DATA OF % IMPURITIES PRESENT IN ETHYLHEXYLGLYCERIN

Name of the impurity	Batch Numbers						
	010 EHG 0716	011 EHG 0716	012 EHG 0816	013 EHG 0816	014 EHG 1016	015 EHG 1116	016 EHG 1116
2-Ethylhexanol	0.01%	0.03%	0.01%	0.02%	0.01%	0.01%	0.01%
2-Ethylhexyl glyceryl ether	0.05%	0.06%	0.08%	0.07%	0.06%	0.08%	0.06%
Total impurities	0.06%	0.09%	0.09%	0.08%	0.07%	0.09%	0.07%

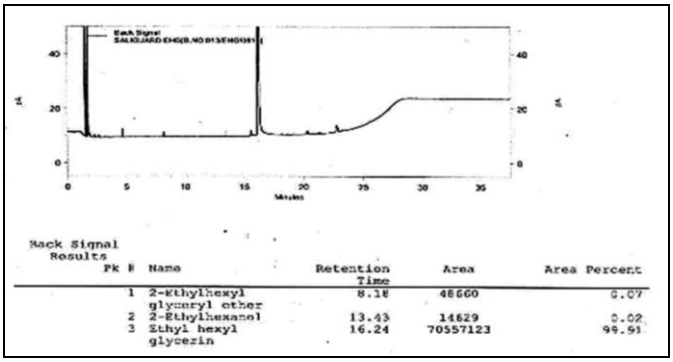

FIG. 8: PRESENCE OF RESIDUAL AMOUNTS OF 2-ETHYLHEXANOL AND 2-ETHYLHEXYLGLYCERYL ETHER PRESENT IN THE ETHYLHEXYLGLYCERIN

CONCLUSION: The manufacturing or synthesis of ethylhexylglycerin can be accomplished by traditional etherification technique. As would be expected an increased chain length translates into greater hydrophobicity. Ethylhexylglycerin, specifically has "limited solubility in water (≈ 0.1%), is highly soluble in organic solvents and has an estimated octanol / water partition coefficient of 2.4.This ingredient function is mostly as surfactants or skin conditioning agents in cosmetic products. Finally, the product is proven as ethylhexylglycerin by spectral characterization. The Purity of the product was >99.0% by this chemical route of synthesis.

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CONFLICT OF INTEREST: The authors declare no conflict of interest and none have received no payment in the preparation of this manuscript.

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