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Formulation, Evaluation of Vitamin E Emulgel for Topical Application with Herbal Enhancers

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Abstract

Vitamin E, an antioxidant with low water solubility and bioavailability, which can protect the skin from atopic dermatitis and other negative effects of sun radiation by scavenging free radicals. The current work aimed to establish and evaluate a microemulsion-based gel considering transdermal drug delivery of vitamin E, herbal enhancers. clove oil, thymus oil and carbopol 940 used as a gelling agent. Emulsion was developed and it was incorporated in gel base. Formulations were assessed for pH, viscosity, spread ability, conductivity, Homogeneity, drug content, FTIR, XRD, DSC, in-vitro drug release and stability studies were conducted. The formulations characteristics showed improved and stable results. F5 showed higher released rate as compared to others formulations, FTIR and XRD confirmed compatibility and stable physical states, while DSC revealed a suitable formulation. In-vitro studies indicated a sustained drug release profile suitable and fit on first release order for transdermal delivery. It can be concluded that the Vitamin E emulgel demonstrated likely as an effective topical drug delivery system. Its stability, enhanced release, and possible physicochemical characteristics showed a promising option for treating inflammatory skin conditions. It was then thoroughly assessed utilizing methods including FTIR, XRD, SEM, and other common tests for efficacy and quality control. In addition to discussing the emulgel's potential for topical drug delivery, this report also covers its synthesis, characterisation, and in-vitro release investigations.

Keywords: Vitamin E, Clove Oil, Thymus Oil, Emulgel, Topical Drug Delivery System.

Introduction

Transdermal Drug Delivery System

Topical medication administration despite its long history, new technologies and approaches are continuously being researched since the skin is the most accessible organ and has the ability to administer several medications more effectively than through other routes of administration. With the most recent developments in knowledge and technology, drugs can now be delivered both topically and systemically for cutaneous purposes, this is among the finest options (1). Topical medication delivery refers to the targeted administration of a formulation via the skin, vaginal, ophthalmic, nasal, and rectal routes in order to minimize side effects and maximize bioavailability (2). Drugs can be accessed through the skin through topical application, which is a different way to get both local and systemic medication effects while reducing the negative

effects associated with other administration methods(3) . Through the use of nanocarriers, which are good and promising outcomes mostly related to the overlap of the cutaneous barrier, the use of nanotechnology in comparison to conventional formulations has been shown to give advantages in the treatment of cutaneous illnesses. When compared to traditional formulations, the use of nanotechnology offers a number of benefits, including improved drug solubility, defence against degradation, greater skin diffusion, and drug retention. Nonetheless, because of the stratum corneum layers, the skin continues to be the greatest barrier to skin penetration(4).

Emulgel

Emulgel are unmatched dermatological preparation with immediate access to the skin for diagnosis and treatment. It is a growing field for topical transport delivery and has limited marketed product (5). Emulgel Emulsions with gels Biphasic system with internal phase, emulsion in an aqueous gel base an innovative vehicle for drug transport predominantly hydrophobic drug (6). Hydrophobic drug is dispersed in the oily phase and then emulsified with the gel base. Emulgel may be oil in water or water in oil and are applied as vehicles to topically deliver drugs. Emulgel may be stabilized with the help of an emulsifying agent. To wash away through the skin and possess a good penetration skill (7). A perfect emulsion is turned into an emulgel by incorporating a gelling agent in the aqueous segment. Emulgel transport diverse drugs to the systemic circulation. Emulgel are bio-friendly, thixotropic greaseless, easily spreadable, easily removable, non-staining, shelf lifelong, transparent and possess good acceptable appearance (8).Applied medication delivery systems can either present as water-in-oil or oil-in-water emulsions, and the inclusion of an emulsifying agent helps stabilize them. These systems have good penetration abilities and can be easily removed from the skin by washing(9).

Vitamin E

For over fifty years, dermatologists have utilized vitamin e as antioxidant in their practices(10). Vitamin E Tocopherol was first identified by Herbert in 1922 and by Evans and Katherine bishop in 1936. It was given the Greek name tocopherol, which means "offspring" (tocos) and "to bring for" (pheros) (11).Tocopherols' primary source of antioxidant action is their capacity to transfer phenolic hydrogens to lipid free radicals, thereby obstructing the oxidation process (12). Fat-soluble vitamin e was first identified in 1922 and has a number of critical physiological roles, including those of an antioxidant, immunoregulatory, anti-inflammatory, and neuroprotector. Its limited water solubility combined with its severe sensitivity to light, oxygen, heat, and alkaline environments can limit the applications of vitamin (13). The aim of the study was formulation, physiochemical characterization of antioxidant Emulgel Vitamin E (Alpha Tocopherol Acetate) for topical application with herbal enhancer.

Materials and Methods

Materials

Vitamin E (Active Pharmaceutical ingredient) was provided by Martindow Marker. Carbopol 934, methyl paraben, propyl paraben, Tween 20, Tween 80, Clove oil and thymus oil were obtained from pharmaceutical laboratory of UOB, cellulose membrane from sigma Aldrich. All other chemicals were used of standard grade.

Preparation of vitamin E (Tocopherol) loaded microemulsion

Various formulations were prepared in which the quantity od drug vit e (5%) w/w, oil phase (10% w/w), surfactant and co-surfantant (50% w/w) in ratio 1:2 penetration enhancer 0.2 %w/w and deionnized water (35 % w/w).

Preparation of vitamin E (Tocopherol) micro emulsion using various oil phases

Formulation of Blank Microemulsion with thymus oil and clove oil

By combining isopropyl alcohol, ethanol, surfactant and co-surfactant with tween 20 /Tween 80 in a 2:1 ratio, a 5.0 g surfactant mixture would be manually created. A surfactant would be added to 1g of thymol oil and clove oil and the mixture would be vigorously stirred with a magnetic stirrer. At room temperature, 3.8g filter water would be gradually adding while being uniformly stirred to create a 10g microemulsion. Lastly 0.2g dimethyl sulfoxide would be add to the microemulsion as a skin penetration booster(14).

Ethanol and tween 20 (1:2)

Vitamin E microemulsion comprising clove oil (F1 , F2 and F3)

The ethanol surfactant, co-surfactant, and tween 20 would be manually mixed in a ratio of 1:2 to create surfactant combination. With the aid of magnetic stirring, the 5.0 g surfactant combination would be introduced to 1.0 g clove oil and vigorously mix to create a microemulsion, then 0.5 g vitamin e would be combined with a mixture of oil-surfactant until completely dissolve. 3.3g Filtered water would be gradually added at room temperature while being continuously stirred at 1200 rpm to produce 10g micremulsion. 0.2 g Dimethyl sulfoxide would be added to the microemulsion as a skin penetration booster (15).

Vitamin E Microemulsion comprising thymus oil (F4, F5 and F6)

Ethanol surfactant, co surfactant, and tween 20 would be manually mixed in 1:2 ratios to create the surfactant combination. A 5.0g surfactant combination would be added to 1.0 g thymol oil, and the mixture would be vigorously mixed while being stirred by a magnetic field. Next, 0.5 g vitamin e will be added to the oil-surfactant combination and stirred until completely dissolved. At room temperature, 3.3g filtered distilled water would be added completely while being continuously stirred at 1000 rpm to create 10g microemulsion. at last 0.2g dimethyl sulfoxide would be added to the microemulsion as a skin penetration booster (15).

Ethanol and tween 20 (1:2)

The same process as in method (a) would be used to create a microemulsion containing thymus oil and clove oil (15).

Preparation of gel bases and microemulsion based gel of vitamin E

Development of carbopol 934P

To create gels based on carbopol 934P, 1.0 g of carbopol would be gently dissolved in 17 g distilled water while being continuously stirred (600 rpm) for two hours at room temperature. Triethylamine would continue to be added until the gel formed, and the pH was adjusted between 4 and 7 (16).

Formulation of carbopol 934 comprising microemulsion without active drugs

82.0g formulate a drug-free polymer-based gel-holding microemulsion. Microemulsion (without vitamin e) would be gently mixed with 18.0g carbopol 934 gel bases using different rpm (500,100,2500), individual formulation for 10, 15, and 20 minutes, respectively, at room temperature to get 100g polymer gel having microemulsion without vitamin e (15).

Formulation of carbopol 934 comprising microemulsion with Vitamin E

82.0g of microemulsion vitamin e was mixed with 18.0g of base gel of carbopol at 500,1000 and 2500 rpm for 15 minutes at room temperature to get 100 g formulation containing vitamin e microemulsion and based gel.

Calibration Curve

To prepare the Vitamin E standard curve, a stock solution was prepared. Accurately weigh 10 mg alpha tocopherol in 50 ml V.flask and dissolve in ethanol to make the volume up to the mark. Diluted 5 ml of this solution in to 100 ml V.flak and make the volume up to mark with ethanol. From this stock, serial dilutions were prepared at concentrations of 0.005, 0.01, 0.015, 0.02, 0.025, 0.03 and 0.035 mg/ml. Diluted 5 ml of this solution in to a 25 ml flask, evaporate dryness and dissolve in 10 ml ethanol and 0.5 ml ferric chloride solution and 0.5 ml 2,2 bipyridin and make the volume with ethanol up to the mark and take the absorbance of each dilution was measured at 520 maxima nm using a UV-Visible spectrophotometer (Shimadzu UV-1601, Japan) [16]. The graph for linearity is delineated in Figure 1.

Evaluation of vitamin E Emulgel

Physical Evaluation

The physical attributes of the formulation such as appearance, consistency and colour was assessed (17).

pH

The pH of the prepared Emulgel was determined by calibrated pH meter (18)

Viscosity

Viscosity measurements for the different formulations were conducted, using a Brookfield RVDV Ultra Programmable Rheometer (Brookfield Engineering Laboratories, Middleboro, MA) fitted with a CP41 spindle. The measurements were taken at various rotational speeds at a controlled temperature of 25°C. Each sample was tested in triplicate, and the mean value was calculated (19,20)

Consistency

The consistency of the emulgel was assessed using the dropping cone method. In this technique, a cone attached to a weighted rod is positioned centrally within a gel-filled container, equidistant from the container's edges, with an initial vertical separation of 10 cm. The depth of penetration into the gel after 50 seconds was used as an indicator of the formulation's consistency (19,20)

Homogeneity

A sample containing vitamin e emulgel was evaluated visually for homogeneity. To look for lumps, thin, transparent glass tubes filled with gel are examined under a light (19,20)

Spread ability

The Spreadability of each formulation was determined in the diameter label by weighing the formulations after they were placed on a 10g microscopic slide and then pack in on another 10g microscopic slide. Consolidation between two slides was then used to measure the diameter, and a formulation circle was created. The spread of a 0.5 g preparation following the contrast of two 10-g microscope slides was used to assess the Spreadability of each formulation (19,20)

Centrifugation
A centrifuge machine was used to hold 5g of formulation in tubes, which were then circulated at 3000 rpm for 30 minutes in order to determine the phase separation test (19,20)

Drug Content (Assay)
To quantify the formulated vitamin e emulgel, 1 g sample in 250 ml Stoppard flask add 30 ml ethanol,3ml of 90 % potassium hydroxide solution and 0.1 g of pyrogallol and saponify by reflex in for 30 minutes on a steam bath allow to cool and transfer to the separating funnel extracted with 30 ml ether thrice. Wash the combine phases free from alkali with water then transfer the ether phse into 250 ml flask and dilute with ether up to the mark. Diluted 5 ml of this solution into a 25 ml flask, evaporate dryness and dissolve in 10 ml ethanol and 0.5 ml ferric chloride solution and 0.5 ml 2,2 bipyridin and make the volume with ethanol up to the mark and take the absorbance using a calibrated UV-Visible spectrophotometer at maximum 520 nm (21)

In-vitro Drug Release Study
An in vitro drug release study was performed utilizing a Franz diffusion cell apparatus (PermeGear, USA) A synthetic cellulose membrane was securely placed between the compartments of the Franz cell, receptor compartment was filled with phosphate buffer up to 12 mL and ethanol mixture (75:25), which served as the receptor medium. A 1.0 g portion of the microemulsion-based gel was applied to the donor compartment, of the Franz cell. Receptor compartment was maintained at a constant temperature of 37°C during the experiment. At predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, and 12), 1 mL aliquots were taken from the receptor medium and immediately filled with an equal volume of fresh medium pre-equilibrated at temperature of 37°C. Sample analysis was carried out using UV-Visible spectrophotometry, following the method described by (22,23).To ensure reproducibility and account for variability across the six Franz diffusion cells, each test were performed in triplicate.

In Vitro Release Kinetics of Emulgel
The amount of substance impregnated was determined and identified using the spectroscopic technique. The drug dosage (5.0mg) in the receptor sample was collected and measured at specific time intervals between 0 and 12 hours." For each formula, the linearity regression research and the drug impregnation release threshold were assessed. To determine whether the drug release followed zero-order, first-order, Higuchi, Korsmeyer-Peppas, or Hixon-Crowell diffusion models, the correlation coefficient (r) was calculated (22,23). It is carried out for every formula. Complete computations were performed using a verified software application, DDSolver for Microsoft Excel 2007. In relation to the following kinetics equations.
$Qt = Qo + K_0 t$ (Zero order)
$\ln Qt = \ln Qo + K_1 t$ (First Order)
$Qt = K^H\sqrt{t}$ (Higuchi Model)
$Mt/M\infty = Kt^n$ (Korsmeyer-Peppas Model)
$Qt / Qo = K_k t^n$ [13]. (Hixson–Crowell Model)

Fourier Transform Infrared Spectroscopy (FTIR)
FTIR analysis was performed to evaluate the compatibility between the drugs and excipients in the formulation. FTIR spectra were measured in the range of 4000–400 cm^{-1} using a FTIR (Perkin-Elmer, USA). The samples were prepared by mixing the components and analyzed under the same conditions as the pure drug and excipient formulations (21).

X-ray Diffraction (XRD)

The transparent nature of emulgel was evaluated using X-ray Diffraction analysis. An X-ray diffractometer (X'Pert Pro, PANalytical, Netherlands) was used to obtain the X-ray diffraction patterns of the test materials. The 2θ range was between 5° and 40° (16).

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry would be done by using a DSC apparatus (21)

Stability Studies

Stability data formulations were assessed at various storage conditions. Samples were stored for three months in (freezer), at 0 ± 1°C in (refrigerator) at 8 ± 0.1°C in (incubator) at 25 ± 0.1°C and in at (incubator) 40 ± 0.1°C Throughout this period, formulations were examined for alterations in physical form, homogeneity, consistency, and pH (22,23).

Statistical Analysis

Kinetic data analysis was conducted using DD Solver, an add-in for Microsoft Excel 2007. An ANOVA calculation was performed using SPSS software (version 18.0, IBM, USA) (22,23). The data would be adjusted with kinetic models

Results and Discussion

The formulation's appearance, color, pH, homogeneity, Spreadability, phase separation, drug content, and consistency were determined (Table 1). The liquefaction, colour, and other parameters of the formulations were all comparable, and the pH was also satisfied. The formulations' pH ranged from 5.5 to 6.4, which is comparable with the pH range used in earlier research on Vitamin E microemulsion-based gel topically in relation to the pH range of normal human skin (4.5 to 6.5) (20, 23). Over the course of ninety days, consistency and Spreadability were investigated. Between 5.66 and 6.43 g/cm/s, the Spreadability varies slightly with shearing pressure. The lack of lumps assured homogeneity. The drug concentration of Vitamin E ranged from 97.12 to 98.76%, and the gel based on microemulsions demonstrated good homogeneity. Convenient outcomes for transdermal application are suggested by the total physical examined factors. The results obtained from conducting stability tests for three months at 25 ± 1°C and 40 ± 1°C were satisfactory and confirmed that the formulation is adequate at (25 ± 1°C) as the percentage of drug left over is not decreased over 10% (20). The standard deviation findings at the end of three months also clearly show that the standard deviation was somewhat higher at 40°C and outside of normal and reasonable ranges, while the standard deviation was smaller at 25 ± 1°C and within a sufficient range. Therefore, it was determined that formulations predict the standards needed to generate the emulgel, which is the subject of interest in extent stability experiments, at 25 ± 1°C.In this investigation, 180 µm thick 0.025-µm cellulose membranes were used, and statistical analysis revealed that the membranes had good release. The highest amount released (70.993%) was displayed by formulation (F5). Which was formulated in in enhancer Thymus oil? This result is similar with previous research by Gul et al., in emulgel formulations (25). The first order permeation model was applied to the data from the highest release of all the formulation discussed in table 2. Figure 2 shows how Vitamin E is released from the transdermal preparation and through the cellulose membrane. The outcomes of the result showed that the amount of drug released through each formulation after 12 hours of investigation was recorded in the receptor solvent contained cellulose membrane (54.831–70.993%).

Figure 1: Calibration Curve of Vitamin E

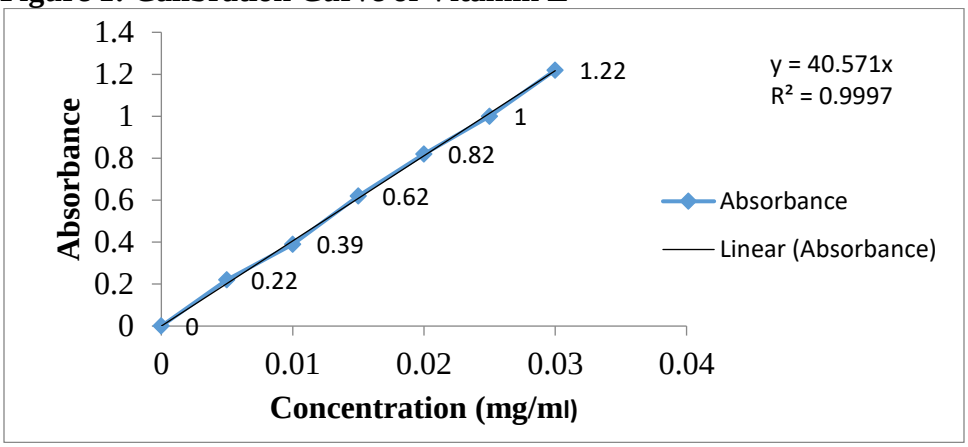

Table 1: Physicochemical Characteristics of Formulations Vitamin E mulgel

Formulations	pH	Color	Homogeneity	Spreadability (g.cm/s)	Phase separation	Consistency	Drug content (%)
F1	5.5	White	Good	5.66	None	Good	97.12
F2	5.7	White	Good	5.85	None	Good	98.00
F3	5.9	White	Good	5.95	None	Good	97.30
F4	5.6	Light yellow	Good	6.14	None	Good	98.11
F5	54	Light yellow	Good	6.24	None	Good	97.21
F6	6.4	Light yellow	Good	6.43	None	Good	98.76

Figure:2 Release of Vitamin E emulgel 0.5% (W /V) via cellulose membrane

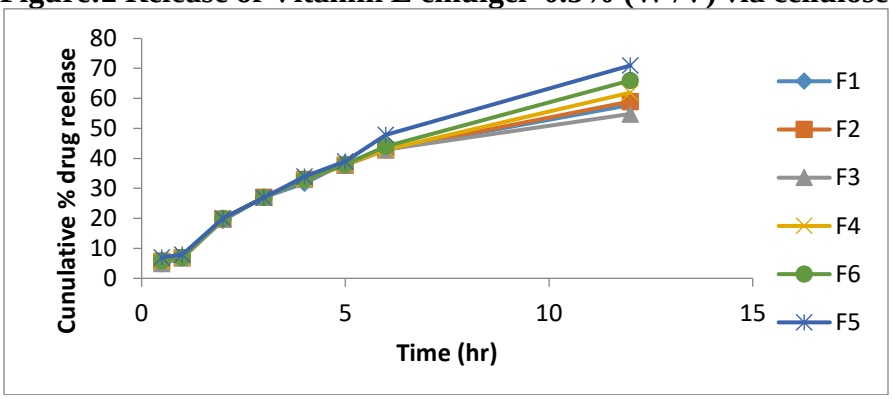

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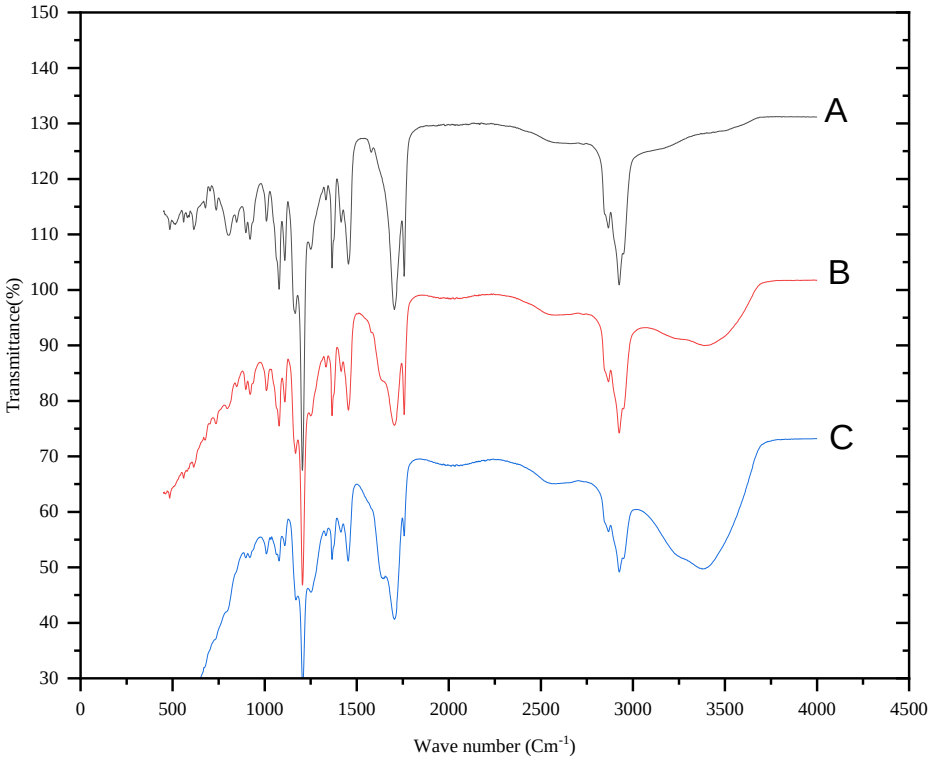
Table 3: Vitamin E Release from the Formulations Using a Cellulose Membrane

Formulation type	Zero (0) Order	First(1st) Order	Higuchi	KorsmeyerPeppass	Hixon-Crowell
F1	0.9445	0.9848	0.9909	0.9830	0.9756
F2	0.9506	0.9878	0.9927	0.9860	0.9796
F3	0.9276	0.9751	0.9845	0.9768	0.9634
F4	0.9616	0.9930	0.9937	0.9900	0.9868
F5	0.9796	0.9980	0.9970	0.9948	0.9968
F6	0.9729	0.9967	0.9954	0.9934	0.9931

FTIR Analysis

No expressive interaction between the drug and excipient was noticed by FTIR for Vitamin E Emulgel formulation. Vitamin E was observed with retention of characteristic peaks at 1420 cm^{-1} corresponding to C=O stretching while at 2900 cm^{-1} with retention of N-H stretching peak in the spectrum for vitamin E; it thus, depicts their stability within the emulgel matrix

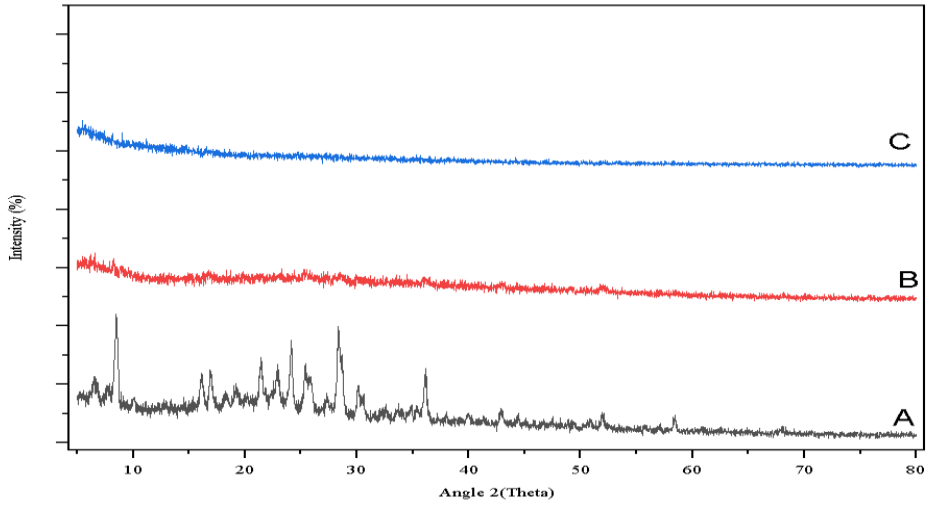
Figure:3 FTIR spectra of Vitamin E drug A, Carbopol B, Formulation F5 is C



XRD Analysis

The emulgel formulation shows a decrease in the crystallinity of vitamin E through its XRD pattern in formulations, thus depicting an amorphous solid dispersion formed that can significantly enhance the drugs' solubility

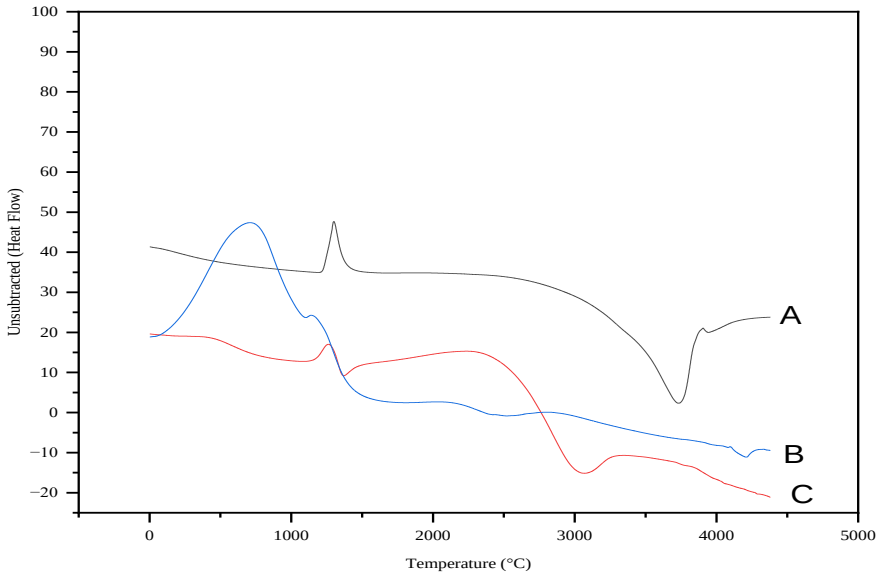
Fig.4 X-ray diffractogram of Vitamin E drug A, Carbopol B, Formulation F5 is



DSC

DSC studies showed that the results revealed no incompatibility between the drug and excipients as shown in Figure 5.

Figure5: DSC of Vitamin E drug A, Carbopol B, Formulation F5 is C



Conclusion

Transdermal drug delivery would be utilized widely in future to impart best patient compliance; Vitamin E loaded microemulsion drugs in water soluble gel bases, developed for best stability. The prepared emulgel formulation showed satisfactory physicochemical properties, best affinity for the membranes and stability with a controlled release profile, which promises this formulation for the treatment of Vitamin E disorders. Formulations data together promote the

suggestion that microemulsion based gel formulations showed potential novel delivery systems to improve the release and stability of Vitamin E

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Conflict of Interest
None

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