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Curcumin-Non-Aqueous Gel - A Newer Paradigm For The Treatment Of Skin Cancers Via The Topical Route

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ABSTRACT

Curcumin is a novel phytochemical compound proven to be effective in treating many types of cancers, including skin cancer. But its therapeutic applications are limited due to its poor aqueous solubility, stability, and permeability. Methods: To overcome these problems, a novel non-aqueous gel formulation loaded with curcumin was developed for topical administration, using Versagel as the gel base, and its ex vivo permeability characteristics were evaluated. Results: The formulations showed a good spreadability, with 18.6% and 23-40% of the drug released within 24 hours of ex vivo studies. The drug release data were fitted to the Higuchi model and the Korsmeyer-Peppas model. The rate of drug release followed first-order kinetics, and the mechanism of drug release was found to be pure Fickian diffusion. Stability studies revealed that curcumin was stable at room temperature, with a calculated half-life of 1506 days. No skin irritation was observed in the skin irritation test. Conclusion: It is concluded that for drugs unstable in aqueous physiological environments, with poor permeability and oral bioavailability, incorporating them into a non-aqueous topical gel (Versagel) represents a novel approach to enhance their stability and therapeutic efficacy in skin cancers.

Keywords: Topical gel, non-aqueous gel, versagel, ex vivo studies.

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INTRODUCTION

Malignant lesions on the skin are referred to as skin cancer and have become epidemic globally, and depending on the region, the type, and intensity of this disease will change. There are two types of skin cancers: melanoma skin cancer and non-melanoma skin cancer.[1] Various treatment modalities are excision biopsy, chemotherapy, immunotherapy, photodynamic therapy, electrocautery, and radiotherapy. All these methods have many unwanted side effects that affect the patient's quality of life and physical well-being. Based on the existing evidence, it is clear that curcumin induces apoptosis and inhibits the proliferation of both melanoma and non-melanoma cancer cells. It also inhibits angiogenesis and metastasis. It modulates the NF-κB, STAT3, and MAPK pathways, thereby preventing the process of carcinogenesis. However, curcumin is a poorly soluble and poorly orally available drug due to its limited absorption, poor stability in aqueous and alkaline media (physiological pH) and it also has limited permeability into the skin. [2, 3] Several nanoformulations of curcumin have been developed, but they require expensive materials and processes. It is hypothesized that when curcumin is incorporated into a non-aqueous gel, such as Versagel, its stability can be enhanced. The Versagel protects curcumin from degradation, improves patient compliance due to its ease of application, non-irritating nature, and transparency. It maintains therapeutic drug concentrations at the tumor site over a prolonged period and, owing to its occlusive nature, enhances the penetration of the drug into superficial tumors. When applied topically to skin cancers, the drug permeates deep into the cutaneous tissue, thereby enhancing its efficacy. Hence, the present study aims to create a cost-effective and straightforward formulation using conventional methods for preparation. The primary objective is to develop a topical curcumin gel by loading the curcumin into Versagel and to study the permeability of curcumin from the gel by ex vivo permeability studies.

MATERIALS AND METHOD

Materials: Versagel® ML 1600 T received as a gift sample from Glen Corp (Calumet Penerco distributor, Mumbai, India). Sesame oil, tween 80, glycerin, and butyl hydroxytoluene were purchased from Sri Sai Scientific Traders, Tarnaka, Hyderabad. Curcumin was purchased from Merck, India.

Method

Analytical Method: A stock solution of 1 mg/mL of curcumin in methanol was prepared. Quality control standards with concentrations ranging from 2 to 10 µg/ ml were prepared using the stock solution. Standard solutions in concentrations of 2, 4, 6, 8, and 10 µg/ml were prepared. A spectrum was taken for the median concentration solution using a UV-Visible spectrophotometer

with a wavelength range of 200 to 1100 nm to determine the λmax. At the chosen λmax, the absorbance was measured for all the working standards. The procedure was triplicated, and the average absorbance values are calculated. Calibration was constructed by plotting concentration vs absorbance.

Loading of curcumin into Versagel: The Versagel ML series was used as the gel base, and the compositions are listed in Table 1. The drug and butyl hydroxytoluene (BHT) were dissolved in sesame oil. The desired quantity of Versagel was transferred into a 10 mL beaker and placed on a magnetic stirrer with a hot plate. The rpm was set at 100. The temperature was maintained at 55ºC. The drug solution in sesame oil was slowly incorporated into the gel. Finally, glycerol was added slowly, the mixture was filtered, and stirring was continued for 15 minutes. A smooth, easily spreadable, non-aqueous gel with uniform distribution of the drug was obtained.

Table 1: Compositions of curcumin non-aqueous gel (curcumin-loaded Versagel formulations)

Formulation code/name of the ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Curcumin (gms)	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02
Versagel ML 750 T(gms)	0.5	-	4.5	-	-	1.5	-	1.5
Versagel ML 1600 T(gms)	-	0.5	-	4.5	3	1.5	3	1.5
Sesame oil (gms)	0.923	0.923	0.923	0.923	0.923	0.923	0.923	0.923
BHT (%)	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075
Glycerol (gms)	0.631	0.631	0.631	0.631	0.631	0.631	0.631	0.631
Tween 80	-	-	-	-	-	-	0.55	0.55

Evaluation of gel

The curcumin non-aqueous gel was evaluated for skin irritation, spreadability, drug content, in vitro drug release, and stability.

Skin irritation test

The gel was applied to the arm and observed for Inflamed skin, Scratch marks, Bumps, spots, or blisters, Dry, cracked skin, and Leathery or scaly patches after 45 minutes, 24 hours, and 48 hours.

Spreadability test

The spreadability apparatus, consisting of two glass slides with two pans on each side set on a pulley and a wooden board with a scale, was used to calculate spreadability. A 100 gms weight was placed on the glass slide for five minutes in order to compress the extra sample to consistent thickness after it had been sandwitched between the two glass slides. The pan was filled with weight (250 gms). Spreadability was measured by measuring the number of seconds needed to separate the two slides.

$S = m * l/t$

m – weight tied on upper slide

l – length of glass slide

t – time in s

Drug content

A quantity of gel equivalent to 1 mg of drug was transferred into a volumetric flask, and the volume was made up to 10 mL with methanol. The drug was extracted into methanol by vigorous shaking, filtered, and diluted to yield a solution with a concentration of 10 µg/mL. The absorbance was then measured at λmax, and the concentration was determined from a calibration curve. The percentage drug content was calculated using the following formula

$$\%\ drug\ content = \frac{concentration \times dilution\ factor}{label\ claim \times 1000} \times 100$$

Ex vivo drug release studies

The Franz diffusion cell was used to carry out the in vitro drug release studies. A piece of goat skin was obtained from a slaughterhouse and placed in ice to prevent deterioration. It was then brought to the laboratory, and the hair was removed using Veet and cleaned with a pH 7.0 phosphate buffer solution. Franz diffusion cell was taken, 17.5 ml of phosphate buffer pH 7.0 was transferred into the receptor compartment containing the bead, and the skin was mounted between the receptor compartment and the donor compartment. A quantity of gel equivalent to 1mg of curcumin was uniformly spread on the skin. The entire assembly was placed on a magnetic stirrer at 50 rpm and a temperature of 37 °C. One milliliter of samples was withdrawn periodically at time intervals of 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 24 hours, and an equal volume of buffer was replaced. The samples were diluted with buffer, and absorbance was measured against a blank. The concentration was determined from the calibration curve, and the cumulative amount of drug released was calculated from the following formula

$$cumulative\ amount\ drug\ released = \frac{conc \times vol\ of\ diffusion\ medium \times dilution\ factor}{1000}$$

$$Cumulative\ \%\ drug\ released = \frac{amount\ calculated}{labled\ claim} \times 100$$

From the dissolution data the order of drug release, the rate of drug release were determined by applying mathematical equations like zero order and first order equations. The mechanism of drug release was determined by plotting Higuchi and Korsmeyer Peppas graphs.

Stability study

The upturned formulation F5, based on drug content, in vitro drug release, and spreadability, was transferred into an amber-colored glass bottle, tightly capped, and stored at room temperature

under shelf conditions for two months. Drug content was determined for every week, and shelf life was calculated.

RESULTS AND DISCUSSION

From the spectrum, the Lambda max (λmax) was found as 428nm, the correlation coefficient was 0.9976, and the linear equation was y = 0.1522x. Curcumin obeyed the Beer-Lambert law in the concentration range of 2 to 10 µg/ml, following the Beer-Lambert law.

Penerco R Versagel technology has been widely used in recent years in various cosmetic, pharmaceutical, and personal care products worldwide. Because this technology enables the thickening and gelling of hydrocarbon materials with an infinite number of customized rheological properties, such as being clear and non-discoloring upon aging, hydrophobic, and thermally reversible without syneresis, they are available in multiple viscosity ranges and are compatible with many ingredients. These gels are easier and safer than those made from metal stearates or fumed silica, and they also provide fragrance retention and waterproofing properties. However, their application in the delivery of drugs for transdermal is not reported. The Versagel ML products, based on C12-15 Alkyl benzoate, provide a light, dry, and non-greasy skin feel. They provide superior solubility, broad ingredient compatibility, and waterproofing characteristics. Other additional benefits include suspension and stability of active principle ingredients such as organic sunscreen agents and topical pain relievers. Therefore, Versagel ML 750 and ML 100T were selected for the present study. These gels can be used in the concentration range of 5 to 70% depending on the specific application. In the present study, concentrations of up to 45% were used. Sesame oil is used to prepare the drug solution, which is then incorporated into the gel. It can also act as a permeation enhancer. Glycerol was added to facilitate the flexibility and spreadability of the gel. Tween 80 was also incorporated to enhance the permeability of the drug.

Among the Versagel ML 750 T and Versagel ML 1600 T, the latter had a better incorporation efficiency of oil and good spreadability. With increasing gel concentration, viscosity increases, allowing a larger amount of drug solution to be incorporated. When tween 80 was included in the formulation, the drug loading efficiency was increased. Formulation 5 had a good average spreadability of 18.6 compared to other formulations, and the results were given in **table** 2

Table 2: Physicochemical properties of Curcumin non-aqueous gel

Formulation code	% Drug content	Spreadability
F1	-	-
F2	-	-
F3	69.83	17.24
F4	54.7	15.46
F5	68.74	18.6

F6	66.15	17.35
F7	76.61	18.64
F8	98.26	17.52

Calibration curve and ex vivo drug release profiles were depicted in figure 1 and figure 2

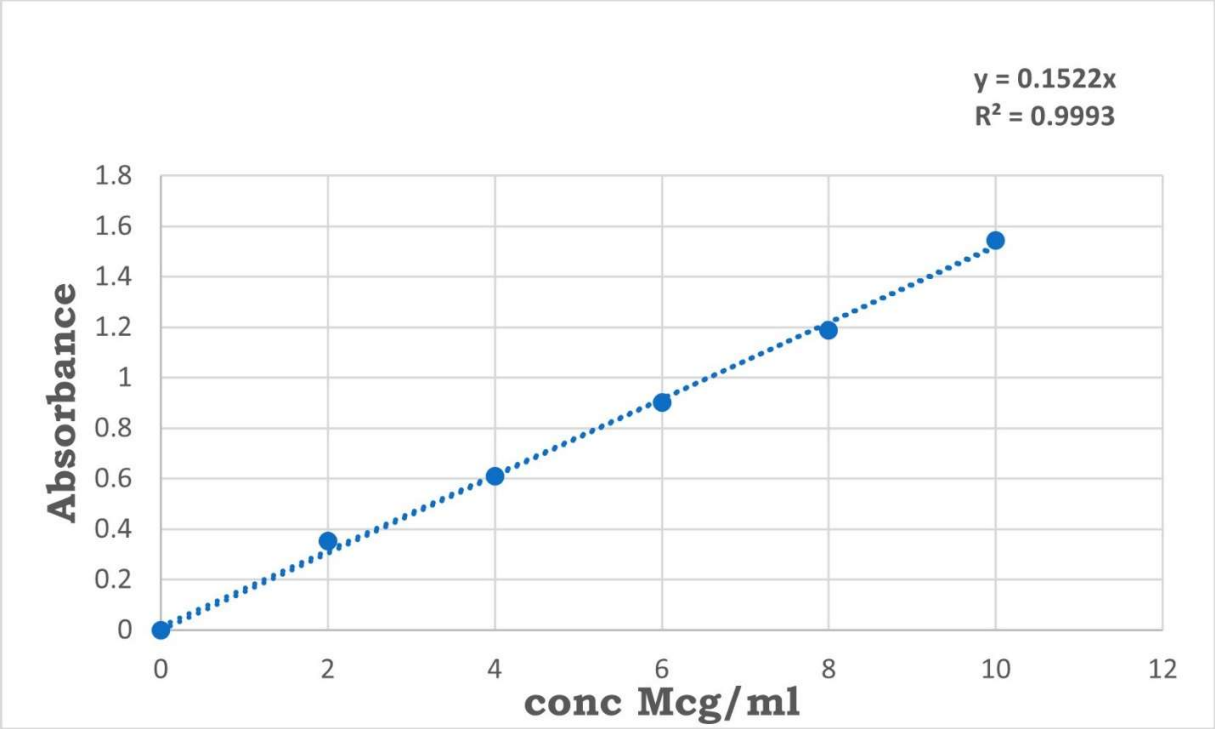

Figure 1: Calibration curve of curcumin in methanol using UV visible spectroscopy

The cumulative percent drug released after 24 hrs was 23-40% for formulations F5 to F8. The rate of drug release followed zero-order kinetics, indicating controlled and sustained drug release, with no lag time observed (within 15 minutes, 1.1% to 4% of the drug was released). The ex vivo drug release data were fitted to the Higuchi model for all formulations. This explains that the mechanism of drug release from non-aqueous gels was matrix diffusion-controlled. A plot of log drug released vs log time yielded a slope n equal to 0.5 for formulations F5 and F6, which shows pure Fickian diffusion. For formulations F7 and F8, the n values are 0.342 and 0.62, indicating slightly non-Fickian behavior; this may be attributed to the presence of surfactant.

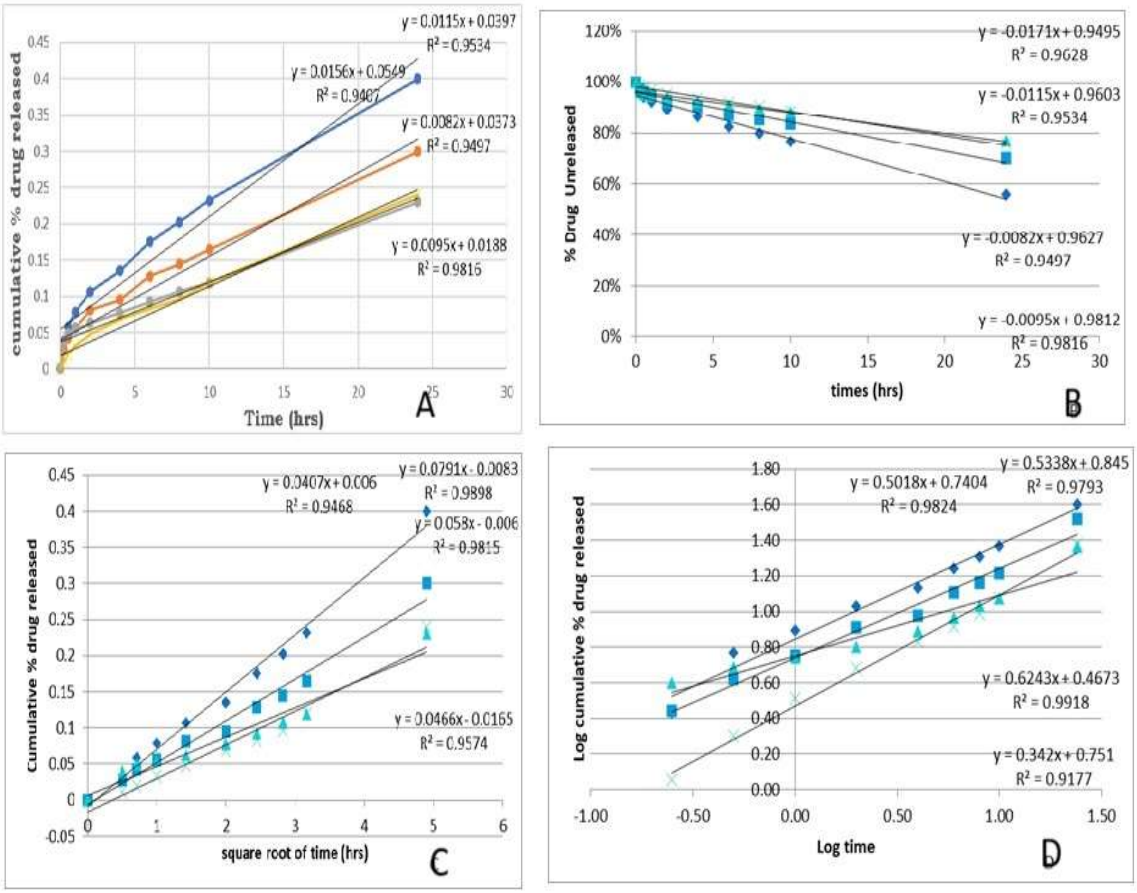

Figure 2: Ex vivo releases profile. A cumulative percent released vs time C Higuchi plot D Korsemeyer Peppas plot

The skin irritation test revealed the safety of the gel, as it did not cause any irritation, scratches, or unwanted reactions on the skin when applied topically.

The F5 formulation was selected based on ex vivo drug release and stability studies. The formulation was stored in an amber colored bottle, screw capped and kept at 40ºC in dark for three months. The percentage of drug content remaining and the log of the percentage of drug content remaining were plotted against time in days. The regression coefficient values were found to be 0.1026 and 0.6, respectively. It states that the rate of drug degradation follows first-order kinetics, and the half-life (t1/2) is calculated to be 1506 days.

CONCLUSION:

With the ex vivo and stability studies of curcumin non-aqueous gel, it is concluded that incorporating curcumin into Versagel is a new approach to increase the curcumin stability and permeability into skin in both types of skin cancers, especially in metastatic melanoma. However, comprehensive preclinical and clinical studies must be conducted to establish this non-aqueous gel

as a promising approach for developing more stable formulations of drugs that are unstable in aqueous and alkaline media and have poor permeability into the skin.

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