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DESIGN, DEVELOPMENT AND EVALUATION OF ULTRA DEFORMABLE LIPID BASED VESICULAR SYSTEM FOR TOPICAL DELIVERY OF PODOPHYLLOTOXIN

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ABSTRACT:- The objective of this study was to design, develop, and evaluate an ultra-deformable lipid-based vesicular system for the topical delivery of podophyllotoxin, a potent anticancer and antiviral agent. Podophyllotoxin's therapeutic application is often restricted due to its poor aqueous solubility, systemic toxicity, and limited skin permeability. To address these limitations, ultra-deformable lipid vesicles were formulated to enhance drug solubility, stability, and penetration through the skin. The vesicles were prepared using phospholipids and surfactants via thin-film hydration and optimized for particle size, zeta potential, entrapment efficiency, and deformability. Key characterization studies, including morphological analysis (TEM), in vitro release, and ex vivo skin permeation studies, were conducted. The optimized formulation exhibited a nanoscale size range (<200 nm), high deformability, and significant drug encapsulation efficiency. In vitro release studies demonstrated sustained drug release over 24 hours, while ex vivo permeation studies confirmed enhanced skin penetration compared to conventional formulations. Furthermore, the vesicles showed superior antiproliferative activity against cancer cell lines and reduced cytotoxicity in healthy cells. This study concludes that ultra-deformable lipid vesicles are a promising delivery system for podophyllotoxin, offering improved topical bioavailability, reduced systemic exposure, and enhanced therapeutic efficacy, paving the way for more effective topical therapies.

Keywords:- Ultra-deformable, Vesicular, Lipid-based, Macromolecules.

INTRODUCTION:-

Podophyllotoxin, a naturally occurring lignan, is widely recognized for its potent anticancer and antiviral properties. It is primarily used in the treatment of conditions such as genital warts and certain cancers. Despite its therapeutic potential, the clinical application of podophyllotoxin is limited due to its poor aqueous solubility, significant systemic toxicity, and low permeability through biological barriers, particularly the skin. These challenges necessitate the development of innovative drug delivery systems to enhance its efficacy and

safety. Topical delivery offers several advantages, including localized action, reduced systemic side effects, and improved patient compliance. However, the skin's stratum corneum serves as a major barrier, limiting the penetration of hydrophilic and lipophilic drugs. Ultra-deformable lipid-based vesicular systems, also known as transfersomes, have emerged as a promising solution to overcome this barrier. These vesicles are designed to be highly flexible, enabling them to squeeze through narrow intercellular spaces and enhance drug penetration. The present study aims to design, develop, and evaluate ultra-deformable lipid vesicles for the efficient topical delivery of podophyllotoxin. By optimizing formulation parameters and assessing their physicochemical properties, permeation potential, and therapeutic efficacy, this research seeks to provide a novel approach for improving the topical application of podophyllotoxin while minimizing associated limitations.[1-4]

MATERIAL AND METHOD

Table No. 1:- Table 1: Formulation table for Ethosomal Preparation (2 ml):

Formulation code	Solvent (ml)	Co Solvent (ml)	Oil Phase (ml)	Surfactant (ml)	Phospholipid (mg)
F1	Ethanol (1.07)	-	Oleic acid (0.28), Lactic acid(0.28)	Span 80 (0.14), Span 20 (0.15)	Lacivia 35 (0.08)
F2	Ethanol (1.36)	-	Lactic acid(0.36)	Span 20 (0.19)	Lacivia 70 (0.09)
F3	Ethanol(1.08)	Ethyal Oleate (0.28)	Lactic acid(0.28)	Span 20 (0.14), Span 80 (0.14)	Lacivia 35 (0.08)
F4	Ethanol(1.27)	Benzyl Benzoate(0.09), Benzyl Alcohol (0.09)	Lactic acid(0.37)	Span 20 (0.18)	-
F5	Ethanol(1.07)	Octanol (0.28)	Oleic acid (0.28), Lactic acid(0.28)	-	Lacivia 35 (0.09)
F6	Ethanol(1.5)	-	Lactic acid(0.2)	Span 80 (0.2)	Lacivia 35 (0.1)
F7	Ethanol(1.36)	-	Oleic acid (0.18), Lactic acid(0.18)	Span 80 (0.18)	Lacivia 35 (0.1)
F8	Ethanol(1.27)	DMSO(0.09)	Lactic acid(0.36)	Span 20 (0.18)	Lacivia 35 (0.1)
F9	Ethanol(1.07)	DMSO(0.08), Ethyal Oleate (0.16)	Oleic acid(0.23), Lactic acid(0.3)	Span 20 (0.16)	-
F10	Ethanol(1.17)	Benzyl	Oleic	Span	Lacivia 35

		Benzoate(0.09), Benzyl Alcohol (0.09)	acid(0.16), Lactic acid(0.1)	65(0.16)	(0.09)
F11	Ethanol(1.08)	Isopropylmyristate(0.28)	Oleic acid(0.28), Lactic acid(0.28)	-	Lacivia 35 (0.08)
F12	Lauryl Alcohal(1.5)	-	Oleic acid(0.2), Lactic acid(0.2)	-	Lacivia 35 (0.1)
F13	Ethanol(1.04)	Lauryl Alcohal(0.46)	Oleic acid(0.2), Lactic acid(0.2)	-	Lacivia 35 (0.1)
F14	Ethanol(1.07)	Octanol (0.15), Isopropylmyristate(0.15)	Oleic acid(0.28), Lactic acid(0.28)	-	Lacivia 70 (0.09)
F15	Ethanol(0.74)	Lauryl Alcohal(0.32), Octanol (0.15), Isopropylmyristate(0.15)	Oleic acid(0.28), Lactic acid(0.28)	-	Lacivia 35 (0.08)
F16	Ethanol(1ml)	-	Lactic acid(0.6)	Span 20 (0.4)	
F17	Ethanol(0.9)	-	Lactic acid(0.6)	Span 20 (0.5)	-
F18	Ethanol(0.8)	-	Lactic acid(0.4)	Span 20 (0.4)	Lacivia 70 (0.4)
F19	Ethanol(0.9)	-	Lactic acid(0.5)	Span 20 (0.6)	-
F20	Ethanol(1ml)	-	Lactic acid(0.4)	Span 20 (0.6)	-
F21	Ethanol(0.96)	-	Oleic acid(0.2)	Span 80 (0.18), Tween 20(0.19)	Lacivia 70 (0.47)
F22	Ethanol(1ml)	-	Lactic acid(0.4)	-	Lacivia 70 (0.6)

Table 2: Formulations selected by screening studies for gel preparation:

Formulation code	Solvent (ml)	Oil Phase (ml)	Surfactant (ml)	Phospholipid (mg)	Water Ratio (1:1)
F18	Ethanol (0.8)	Lactic acid (0.4)	Span 20 (0.4)	Lacivia 70 (0.4)	(1:1)
F21	Ethanol (0.96)	Oleic acid (0.2)	Span 80 (0.18), Tween 20(0.19)	Lacivia 70 (0.47)	(1:1)
F22	Ethanol (1ml)	Lactic acid (0.4)	-	Lacivia 70 (0.6)	(1:1)

Preparation of Ethosomal Gel

Preparation of gel base:

The gel base for all three screened formulation were prepared in three different polymers i.e., Carbopol 980 NF (1.5 % w/w); HPMC 15000 cps (4 % w/w) and Xanthan gum (2.5 % w/w).

Table 3: Composition of Gel bases of Carbopol* 980 NF, HPMC 15000 cps and Xanthan Gum

Ingredient	C_{18}	H_{18}	X_{18}	C_{21}	H_{21}	X_{21}	C_{22}	H_{22}	X_{22}
Sodium benzoate	0.5 % w/w	1 % w/w	0.5 % w/w	0.5 % w/w	1 % w/w	0.5 % w/w	0.5 % w/w	1 % w/w	0.5 % w/w
Benzyl Alcohol	2 % v/v	2 % v/v	2 % v/v	2 % v/v	2 % v/v	2 % v/v	2 % v/v	2 % v/v	2 % v/v
Propylene glycol	5 % v/v	5 % v/v	5 % v/v	5 % v/v	5 % v/v	5 % v/v	5 % v/v	5 % v/v	5 % v/v
DMSO	1 % v/v	1 % v/v	1 % v/v	1 % v/v	1 % v/v	1 % v/v	1 % v/v	1 % v/v	1 % v/v
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

*Add triethanolamine to adjust the pH 7 for gel formation.

Result and Discussion

Determination of Absorption maxima (λ_{max}) in 0.1 N HCl

The stock solution was prepared as per the method described in methodology section and scanned by UV-Visible spectrophotometer. The λ_{max} was found to be 284 nm was taken as analytical wavelength. The UV absorption spectrum of Podophyllotoxin showed peak at 284.0 nm against blank and the same was used for further analysis.

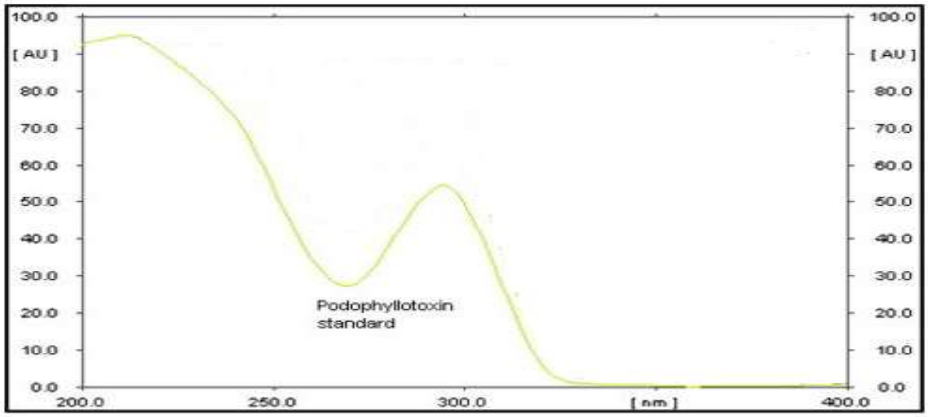

Figure 1: UV Spectrum of Podophyllotoxin in 0.1 N HCl

Calibration Curve of Podophyllotoxin in 0.1 N HCl

The calibration curve and data obtained by the procedure described in methodology section are given in Table 6.1. The data correlation coefficient of 0.999 and the equation of regressed line, y= mx + C depicted below

Table: 4 Calibration Curve Data for Podophyllotoxin in 0.1 N HCl

S.No.	Concentration(µg/ml)	Absorbance(284 nm)
1	1	0.219
2	2	0.41
3	3	0.628
4	4	0.92
5	5	1.062
6	6	1.302
7	7	1.514
8	8	1.72
9	9	1.918
10	10	2.132

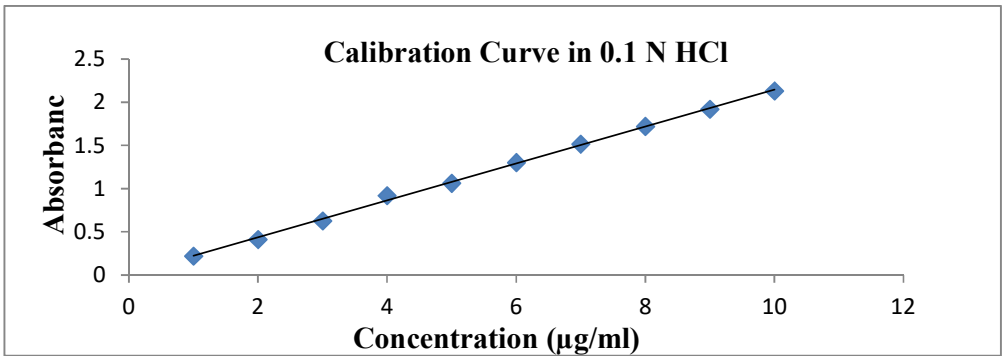

Figure 2: Calibration curve of Podophyllotoxin in 0.1 N HCl

Total percentage of drug released after 8 hr was found to be different among different formulations. Increase in total release from ethosomes was observed with increase in lecithin concentration. However, on further increase in lecithin concentration, the release was found to get decreased.

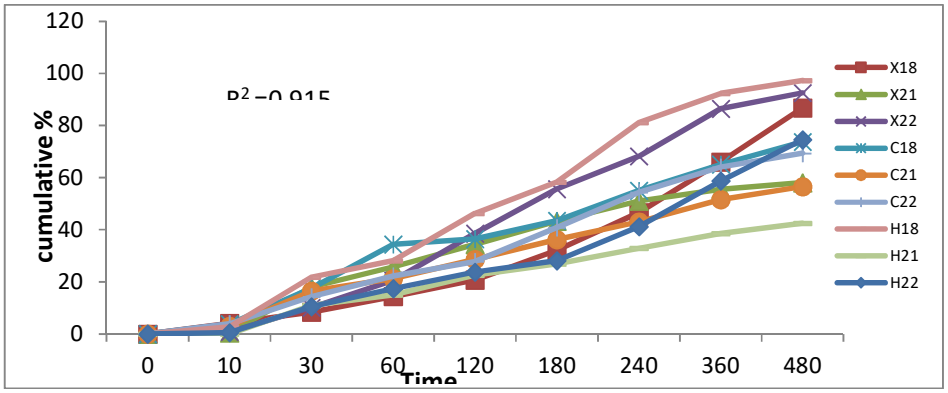

Figure 3: *In-vitro* drug release profile of Podophyllotoxin from different ethosomal formulation

Table:5 Properties of optimized formulation

Gel	Firmness (gm) ±SD	Work of shear (gm.sec) ±SD	Stickiness (gm) ±SD	Work of adhesion (gm.sec) ± SD	Cohesiveness	Gel Strength (gm $mm^{-1}sec^{1}$)
X18	17.50±3.17	05.38±1.29	-13.63±2.87	-13.38±3.21	0.82±0.04	4.37±0.31

CONCLUSION:

Ethosomes have been considered as a possible vesicular carrier for transdermal delivery of Podophyllotoxin. The study confirmed that ethosomes are very promising carrier for the transdermal delivery of Podophyllotoxin revealed from higher entrapment efficiency and release study. In light of the data obtained from experimental work we can expect the ethosome formulation to be safe and very efficient as a drug carrier for as topical delivery of Imiquomod. The aim of current investigation is to evaluate the transdermal potential of novel vesicular carrier ethosomes, bearing Podophyllotoxin, anti-viral drug having limited transdermal permeation. By formulating Podophyllotoxin as an ethosomal formulation, we can control the permeation of drug in which ethanol acts as permeation enhancer. Ethosomal systems are capable of delivering higher amounts of Podophyllotoxin at controlled release rate. It provides better remission from the disease and reduces the duration of therapy.

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