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FORMULATION AND EVALUATION OF TENOXICAM ETHOSOMES AS A NOVEL DRUG CARRIER

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Abstract

The aim of this study is to create an alcohol-based tenoxicam gel for transversal delivery. Tenoxicam is a non-steroidal anti-inflammatory BCSII drug with low solubility and high permeability. It is prepared thermally using alcohol, phospholipids and ethanol. Alcosomes are phospholipid- based elastic nanoparticles containing high levels of ethanol (20-45%), which is known to be highly accessible. Ethanol systems are more effective at delivering the speed and depth of medication to the skin than liposomes or hydroalcoholic solutions. FTIR studies show that there is no interaction between the drug and the additive. Formulation F8 (ethanol 30% v/v and lecithin 1% w/w) was selected as the best formulation due to its small size, encapsulation efficiency, low turbidity, and highest in vitro release. A 3-month stability study was carried out on the F8 formulation using Carbopol 934 base (1,1.5, 2% w/w) at two different temperatures, 25°±2°C and 4°±2°C. The maximum in vitro release rate of carbomer concentration in rat skin at 1.5% w/w is 95.06 ± 0.15%, and the in vitro release rate is 86.65 ± 0.38%.

Key words: tenoxicam, penetrating liposome, ethosome system.

Introduction

Nonsteroidal anti-inflammatory drugs are the most commonly used drugs to reduce pain and inflammation. Tenoxicam is a non-steroidal anti-inflammatory drug that can treat inflammatory diseases such as rheumatoid a rthritis and osteoarthritis, but oral administration is not re commended due to bacterial proliferation, stomach pain and other serious diseases. , improves patzient compliance, prevents first-pass metabolism, and maintains long-term plasma concentrations. The half-life of tenoxicam is 72 hours. (range 59-74 hours), elimination half-life is 30-140 hours. It can synthesize many proteins. Transdermal drug delivery (TDD) has many advantages such as large and easily absorbed area, ease of application and cutting therapy, development of effective d rug molecule delivery technologies, safe access to particles and vesicular carriers. It is designed for use in transderma l drug delivery. Human skin is a good and selective barrier to chemical penetration. However, the skin- based delivery method can provide many advantages such as preventing first-pass metabolism, reducing plasma drug levels, targeting the local activity of active substances, and good patient follow-up. Water-soluble molecules and drugs generally cannot pass throug h the skin. The corneal layer consists of bundles of insolubl e keratin surrounded by cells and a capsule. The corneal la yer consists of 40% protein (mainly keratin), 40% water a nd 15-20% lipids (15% triglycerides and free fatty acids, 25% cholesterol, 50% sphingomyelin) and sma ll amounts of other lipids. While lipids are mostly found ex tracellularly, ibn proteins are both intercellular and intrac ellular. The lipid content of bone tissue provides low perm eability to various external substances while protecting th em. For example, in the vesicle method, liposomes in trans dermal drug delivery have been studied for many purpose s, but instability limits their use in clinical and commercial settings. To increase the stability of liposomes, the concept of proliposomes was proposed. However, these methods

are not effective in delivering transdermal drugs effectivel y due to skin defects, blood vessels, drug leakage, vesicle a ggregation, and fusion.

Recently, Ethosomes, a transdermal delivery system for to pical/transdermal drug delivery, have been developed. Du e to its highly elastic properties, it has an excellent ability t o penetrate human skin, which has a great impact on the d esire of the carrier to be used for local use and export of hy drophilic and lipophilic substances. Alcosomes are soft, ma lleable lipid vesicles composed mostly of phospholipids, hi gh concentrations of alcohol (ethanol, isopropyl alcohol) (20-
45%), and water. Ethosomes were first discovered by Toui tou and colleagues in 1997. An interesting property of this vector concerns its ability to penetrate human skin with hi gh deformability. The physicochemical properties of ethos omes make vesicular phospholipids the vesicle-
forming components of the ethosome system. Ethanol is a n efficient permeation enhancer that is believed to act by a ffecting the intercellular region of the stratum corneum. T he size of that vesicle can be modulated in terms of nanom eters to microns.

Materials and methods

Tenoxicam was purchased from Glenmark Pharmaceutical s LTD, Mumbai, India. Phospholipids/lecithin was purchas ed from S.D. Fine Chemicals. MUMBAI INDIA LIMITED. Eth anol, propylene glycol, methanol and other reagents can b e used at the test level. Animals used:

Male albino mice weighing 180-
220 g were used for skin studies and immunological studie s.

Ethical Approval:

The study protocol was approved by the Animal Ethics Co mmittee of the Narasaraopeta Institute of Clinical Medicin e (NIPS).

Compatibility study:

FT-IR spectrophotometer (Thermos Nicolet FT-
IR system) was used to evaluate possible conditions

Preparation Thermal method

The thermal method is to disperse phospholipids in water. 40°C water bath until a colloidal solution is obtained. Put ethanol and propylene glycol in a separate container and h eat to 40 °C. When both mixtures reach 40°C, add the orga nic phase to the aqueous phase. Due to its hydrophobic str ucture, the drug is soluble in ethanol. The solution was the n added to the phospholipid dispersion and stirred contin uously on a magnetic stirrer (1500 rpm) for 10 min. Finall y, store the preparation in the refrigerator.

Preparation of Gel Matrix accurately weigh Carbopol 934 (1-3% w/v) and disperse in double distilled water (80ml) in a beaker. The solution was stirre d continuously at 800 rpm for 1 hour, and then 10 ml of pr opylene glycol was added to the solution. Neutralize the re sulting small amount of acid by adding 0.05N sodium hydr oxide solution dropwise and continue stirring until the gel becomes transparent. Adjust the gel volume to 100 ml and sonicate in a sonicator bath for 10 min to remove bubbles. Finally, the pH of the gel matrix was adjusted to 6.5. Also p repare the gel containing the active ingredient, add 10 mg of the ingredient and distribute correctly according to the above procedure. The ethosome formulation is fused to th e gel matrix with 0.05% w/w drug to obtain the desired dr ug in the gel matrix.

Preparation of the active ingredient in the Gel Matrix

Preparation of Tenoxicam Common Gel using a similar met hod is used to prepare alcohol. The amount of tenoxicam s hould be administered in this way and ground into a water - miscible gel matrix. The final concentration of tenoxicam in the formulation was fixed at 0.3%.

Add Gel Soak Carbopol 1% w/w in a small amount of water for one hour. 20 ml of ethanolic suspension containing tenoxicam (100 mg) was added to the swollen polymer with continuous stirring at 30 °C until a homogeneous gel was obtained. Then adjust the pH to neutral using triethanolamine and mix gently until a clear and transparent gel is obtained.

Table1: Compositionoftenoxicamethosomes:

FORMULATION CODE	DRUG (%W/W)	LECITHIN (%W/W)	PROPYLENE GLYCOL(%V/V)	ETHANOL (%V/V)
F_1	0.3	0.5	10	10
F_2	0.3	0.5	10	20
F_3	0.3	0.5	10	30
F_4	0.3	1	10	10
F_5	0.3	2	10	20
F_6	0.3	1	10	20
F_7	0.3	2	10	30
F_8	0.3	1	10	30

Table2:FORMULATIONSOFTENOXICAMETHOSOMALAND PLAINDRUG(PD)GEL

GelFormulation Code	Carbopol(%W/W)	Triethanolamine(%w/w)	Phosphatebuffer
G_1	1	0.5	Q.s.
G_2	1.5	0.5	Q.s.
G_3	2	0.5	Q.s.
PD	1.5	0.5	Q.s.

Characterization and evaluation of Alcoholic Gels Physical evaluation

Physical evaluation is based on sensory properties (look/f eel of the drug, smell and other things).

Odor, washability
and soft transition, determination of separate phase and o dor (grittiness, oiliness) properties during use. The rinsea

bility of a gel is determined by applying a small amount of gel to the skin. After washing, check whether the gel is com pletely washed off.

Spread was determined using modified trees and slide tool s. Place the measured gel (0.5 gm) on a round glass slide w ith a diameter of 1 cm; Place the moving plate with the slid es on the fixed glass so that the gel will be squeezed betwe en the two slides for 5 minutes. Record the increase in dia meter due to gel spreading and determine the spread usin g the following formula7.

S= m/t

Where S is the transmission capacity in the sliding glass. M is the weight in grams. T is the time in seconds. Solubilit y Determination:

The solubility of the drug is determined by taking an amou nt of the drug (approximately 1-

2 mg) into a tube weighing 5 ml (water, ethanol, methanol, 0.1). N HCl, 0.1 N NaOH, chloroform and 7.4 pH resistance). Shake vigorously and let it sit for a while. The solubility of the drug in various solvents was found at room tempera ture.

Encapsulation Efficiency

The encapsulation efficiency of tenoxicam ethosomes was determined by ultracentrifugation technology. Place 15 ml of ethanol body preparation in a centrifuge tube and centri fuge at 12,000 rpm for 2 h and measure the total volume of the supernatant. Determine the amount of drug in the pro cess supernatant using a UV spectrophotometer at 224 nm . The encapsulation value is calculated according to the for mula below.

Encapsulation rate = [(Qt – Qs) / Qt] x 100

Here Qt is the additive.

Qs is the amount of drug present in the supernatant.

Skin irritation

The research was done on healthy albino mice. Animals we re divided into 5 groups: sample group, control group and alcohol preparation group (G1 – G3). A 2 cm2 area of the back skin was shaved the day before the study. Formali n was used as the standard stimulus. The study was condu cted for 7 days with one sample per day. At the end of the s tudy, observe the animal for any skin irritation such as ery thema or edema and record the findings.

In vitro diffusion studies

In vitro diffusion studies are performed on cells using Fran z diffusion. The egg membrane acts as a semi-

permeable membrane for diffusion. The Franz diffusion cel l has a receptor chamber with an effective volume of appro ximately 60 ml and an impressive permeability surface are a of

3.14 cm^2. The egg membrane is placed between the donor and recipient cells. Take a 2 cm2 patch, weigh it, and place it on one side of the membrane facing the donor chamber. Neutral receptor phosphate buffer pH is 7.4. The receptor chamber is surrounded by water to maintain the temperat ure at 32 ± 0.5 °C. A thermostatic hot plate with a magnetic stirrer is used to provide heat and the receptor fluid is mi xed via a Teflon-

coated joint vacuum beads inserted into the cell. During ea ch experiment, the sample was removed and replaced with an equal amount of fresh liquid at each test time. The extr acted samples were analyzed spectrophotometrically at a wavelength of 351 nm.

In vivo anti-inflammatory activity

The anti-

inflammatory properties of normal gel and alcohol gel wer e compared with foot edema caused by carrageenan. The a nimals were divided into three groups of four animals eac h. The first group was given a normal control and a gel con taining saline. The second group was given tenoxicam nor mal gel, and the third group was given tenoxicam alcohol g el. 30 minutes after administration of the preparation (0.5 g), 1% (w/v) carrageenan saline solution (0.1ml) was injec ted subcutaneously into the tendon of the right hind paw, and the treatment of rats in the two groups was competitiv e. Assess the percentage of inhibition by measuring the de gree of paw edema with plethysomete (IITC).

Results and Discussion

Analysis of tenoxicam in vesicles plot of the relationship b etween absorbance at 254nm and concentration (µgml) Fi gure to generate the tenoxicam calibration table (Figure 1) . To determine the relationship between the two, the (r2) c orrelation coefficient is calculated and the result is 0.998.

Mathematical form of the relationship

y=0.221x +0.004 between thetwo variablesi.e.,absorbancevs concentration.

Table3:StandardcurveofTenoxicam

S.No.	Concentration(µg|mL)	Absorba
1	0	0
2	2	0.019
3	4	0.035
4	6	0.049
5	8	0.063
6	10	0.079
7	12	0.093

vesicle size:

The vesicle size of ethosomes varies from 134 to 266 nm. The size of vesicles increased when the phospholipid conc entration was increased from 0.5% w/v to 1% w/w and d ecreased when the ethanol concentration was increased fr om 10% w/v to 30% w/w. The vesicle size increases with increasing phospholipid concentration from F1 to F6. Fro m F1 to F8, the size of vessels was found to decrease as th e ethanol concentration increased from 10% v/v to 30% v /v. This may be due to the formation of phases with intert wined hydrocarbon chains. The decrease in size is due to t he ethanol-

induced change in the amount of system and a degree of st eric stability.

Vesicle shape:

The vesicle shape of all alcohol preparations has been fou nd to be spherical with a smooth surface. Turbidity of alco hol formulations was found to range from 200 ± 2.10 to 4 30 ± 1.05 NTU. The data show that turbidity increases fro m F1 to F8 as the ethanol concentration increases from 10 % v/v to 30% v/v. The turbidity of F7 and F8 was found t o be higher than other alcohol preparations.

TABLE4: Results showing Vesicle size, Turbidity. Entrapment efficiency

Formulation code	Vesicle size (nm)	Turbidity (NTU)	Entrapment Efficiency (%)
F1	167	209±2.08	2.16±0.17
F2	151	261±1.05	4.3±0.2
F3	134	280±0.5	6.5±0.47
F4	215	229±1.08	9.2±0.3
F5	221	250±3.30	0.5±0.30
F6	222	265±1.5	1.6±0.15
F7	161	409±1.32	5.5±0.41
F8	257	424±1.02	9.4±0.2

Encapsulation Efficiency

Encapsulation efficiency for all formulations ranged from 2.15 ± 0.17% to 9.4 ± 0.2%. F8 was found to have the best encapsulation efficiency, while F4 had the lowest encapsul ation efficiency. Similarly, the encapsulation efficiency of h ydroethanolic solutions was found to be lower than alcoh ol formulations. Differences between ethanol and phosph olipids in alcohol preparations are related to vesicle size. The data show that the encapsulation efficiency of vesicles increases as the ethanol concentration increases from 10 % v/v to 30% v/v and the phospholipid concentration inc reases from 0.5% w/w to 1% w/w.

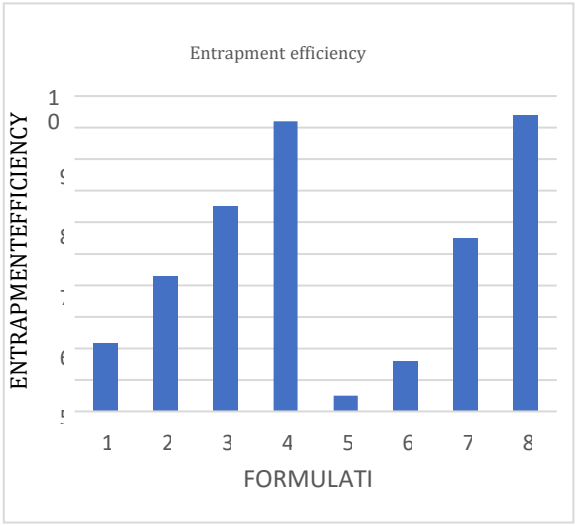

FIG.2:ENTRAPMENTEFFICIENCY

Release profile of alcohol gel formulation

Tenoxicam alcohol gel was prepared in three different con centrations: 1, 1.5 and 2% w/w Carbopol 934. While exam ining the release profile of different alcohol concentration s using water filters and mouse skins. The maximum relea se of G2 in the dialysis membrane was 95.06 ± 0.15% and in rat skin was 80.65 ± 0.38%. In both cases, the results ob tained from the G2 formulation are higher than the results obtained from the G1 and G3 formulations. Since G2 saw t he highest output, it was deemed beneficial to the final de velopment of the design.

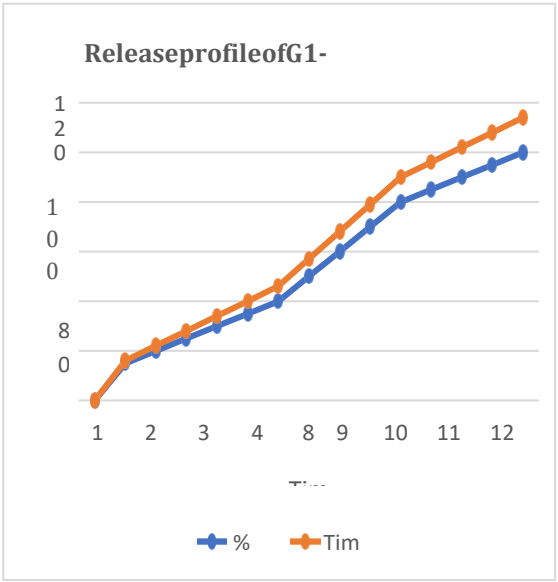

FIG.3: RELEASE PROFILE OF ETHOSOMAL GEL ANDPLAINDRUG GELTHROUGHMICE SKIN

Drug release films from ethosome suspensions
In vitro drug release from tenoxicam ethosomes was perfo rmed in a Franz diffusion cell in phosphate buffer 7.4 at 3 7°C for 24 hours. The 24-
hour cumulative release percentage of preparations F1 to F8 ranged from 38.98 ± 0.36 to 98.65 ± 0.23, respectively. Among all the formulations, F8 was found to be the best fo rmulation with drug release of 98.62 ± 0.23 in 24 hours. D rug release increased as the ethanol concentration was gr adually increased from 10% v/v to 30% v/v. This may be due to ethanol's role as a penetrating agent.
In vitro drug release study
In vitro drug release from ethanol body was checked usin g Franz diffusion cell method and found to be 98.6 ± 0.23 % in 24 hours. The amount of drug released in the first 30 minutes was slightly higher, 14.56±0.12. As the ethanol co ncentration gradually increased from 10% v/v to 30% v/v , the release rate also increased. This may be due to the eff ect of ethanol following penetration.

Table5: In-vitro drug release study of prepared gel formulation

Time(hour)	Formulation code	% Cumulative drug release
0	F1	0
1	F2	38.98±0.36
4	F3	45.56±0.32
8	F4	55.65±0.25
12	F5	68.98±0.14
16	F6	76.65±0.48
20	F7	89.46±0.29
24	F8	98.62±0.23

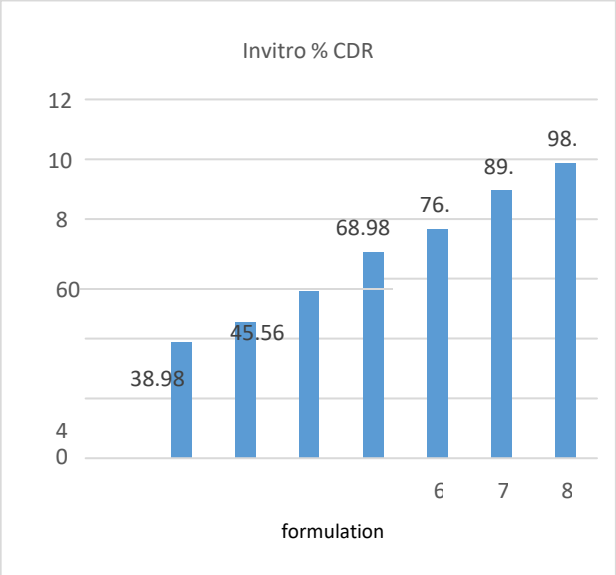

FIG.4: IN VITRO DISSOLUTION STUDY

Table 6: Skin permeation studies for final ethosomal gel formulation

Time (min)	% Drug Permeated
0	0
5	7.20
10	14.15
15	23.80
20	42.40
60	79.65
120	98.30

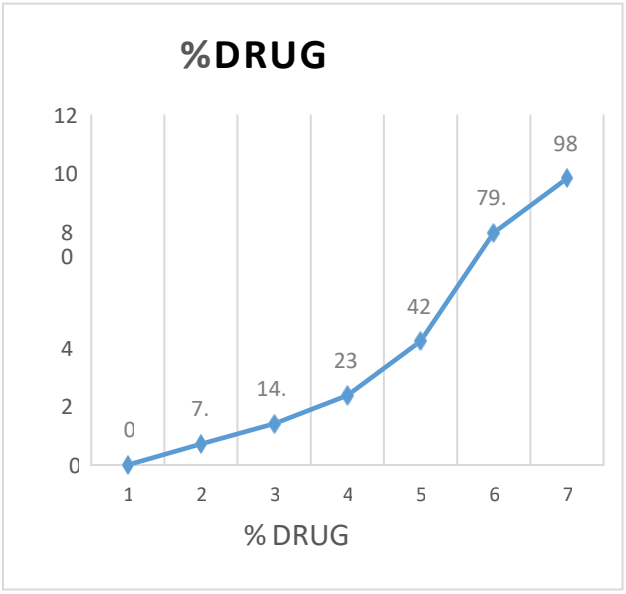

Fig.:4 SKIN PERMEATION STUDIES SKIN IRRITATION Research
In the skin irritation research, formalin was used as the standard irritant, and control group 3 did not use any preparation. The results showed that stimulation of the skin with ethanol stem G1 and G2 resulted in scores of 0.5, 1, and 0 after 8 days. Since the average score in the skin study is less than 2, it can be concluded that alcohol gel does not harm the skin.
FOURIER TRANSFORM INFRARED - RAY SPECTROSCOPY (FT-IR) STUDIES:

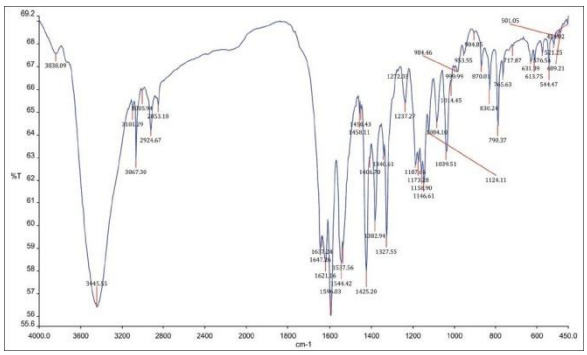

FIG.5 FT-IR OF PURE DRUG TENOXICAM

Conclusion

In this study, 8 types of tenoxicam ethosomes were prepared using thermal methods and their differences were not evaluated. Based on variables such as vesicle shape, vesicle size, and encapsulation efficiency, F8 was selected as the best formulation. Therefore, F8 was added to the gel using Carbopol 934 and 1.5% w/w Carbopol was found to be more effective. The results show that the alcohol solution is more effective than the ordinary gel formula in terms of skin penetration and protective performance. In conclusion, it appears that ethosomes will be excellent and safe drug carriers and excellent drug carriers for topical and local delivery of tenoxicam in clinical practice.

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