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Formulation and evaluation of desonide ethosomal gel

K Seenivasan*, R Priyadharshini, Barish, S Mahalakshmi
Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, Sulur Coimbatore, Tamil Nadu, India

Abstract
Development of novel drug delivery carriers are a necessity to deliver the drugs to target site at a faster rate to overcome the drawbacks of multi-dose therapy, Thereby it reduced the frequency of dosing, increased the bioavailability of drug and increase patient compliance and improve their safety. For drug delivery via dermal and transdermal routes ethosomes have emerged as a non-invasive mean, ethosome is novel lipid carrier, showing enhanced skin delivery. The ethosomal system is composed of phospholipid, ethanol and water. The size of ethosomes varies from few nanometres to micrometres depending on method of preparation and application of techniques like, sonication. Several studies investigated the effect of ethanol on physicochemical characteristics of the ethosomal vesicles. The aim of our investigation was to evaluate the transdermal potential of novel vesicular carrier. ethosomes containing topical Corticosteroid DESONIDE, anti-inflammatory and antipruritic agents were successfully entrapped into the ethosomal vesicles. Apart from ethanol, propylene glycol was also used as permeation enhancer which would improve the solubility and partitioning of drug across the membrane. this formulation produced excellent drug release ensured that this was effective formulation for the treatment of various Skin infections. Including Psoriasis and Atopic Dermatitis.

Keywords: Desonide, ethosomes, ethanol, skin infections

Introduction

India is a country with vast diversity in the climatic and weather conditions. The climate is generally hot, humid and tropical type. This type of climate tends to favour the growth of variety of microorganisms and disease-causing pathogens. Majority of studies showed that occurrence of various diseases and infections caused by such organisms in our country is at very high percentage. Around the world, skin infections have recently emerged as a growing threat to human health, especially in persons whose immune systems are compromised in some way. For example, microorganisms are associated with complex disease entities in complex medical patients. Research on skin diseases focuses on three goals: providing better means of diagnosis, treatment, and prevention of the most important human fungal infections. Objectives leading to the achievement of these goals are grouped in the following five research areas:

- Molecular biology
- Immunobiology
- Pathogenesis
- Therapy
- Genome sequencing and genomics/proteomics

The interest in this has led to work on the developments of novel molecules, delivery systems as well as formulations which can control these skin infections to a greater extent than before. Most of the skin infections appear over the skin, the treatment regimen of these infections always comprises of external application formulations such as creams, ointments, lotions, etc[1]. It's a fact that delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders caused by microorganisms. But apart from that, dermal drug delivery has gained popularity because of its advantages over other routes of administrations such as, it avoids firstpass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration[2].

Vesicles are the structures that are small in size having a bilayer arrangement similar to the natural lipid bilayer structure of our body membrane. They are highly efficient in encapsulating drugs having varied physico-chemical properties. Stratum corneum is regarded as the major hindrance in attaining a good penetration of drugs transdermally and is easily overcome by these vesicular structures[3,4]. Amphiphillic nature of vesicles helps to deliver both hydrophilic as well as lipophilic drugs to their respective targets with relative ease. Liposomes were developed earlier as pioneer model in vesicular delivery system. Vesicles contribute greatly in cellular communication as well as particle transport. Researchers have revealed their conclusion that the vesicular morphology helps them to deliver drugs in efficient manner and vesicles can be tagged for cell specificity, thus producing a targeted action. The liposomes were further modified for better features which lead to the discovery of ethosomes which is considered by many as one of the major advancement and advantage in vesicular research[5,6]. Ethosome was developed in the first place by Touitou and her colleagues' in 1997 [7, 8].

Vesicular systems

- Liposomes
- Niosomes
- Transferosomes
- Spingosomes
- Pharmacosomes
- Virosomes
- Colloidosomes
- Aquasomes
- Cubosomes
- Ethosomes

Ethosomes

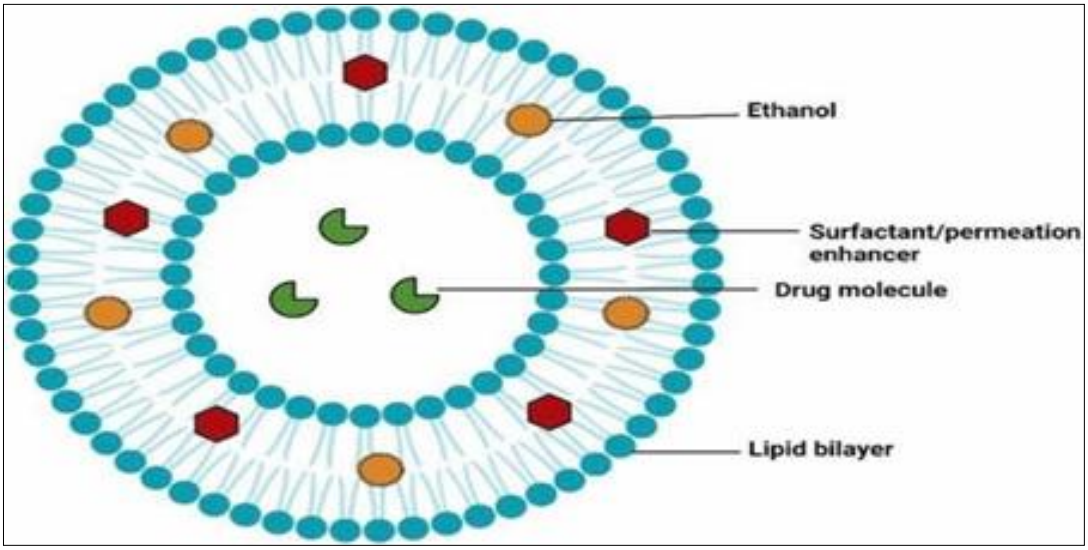

Fig 1: Structure of Ethosome

- Ethosomes are "Ethanolic liposomes
- Ethosomes were developed by Touitou, 1997 and investigated lipid vesicular system containing ethanol in relatively high concentration (20-50%).
- Ethosomes are non-invasive delivery carrier that enable drugs to reach the deep skin layer and/or systemic circulation
- "Soft vesicles'' represent novel vesicles carrier for enhanced delivery through the skin, made of Phospholipids and ethanol (in higher quantity) and water.
- size of ethosomes vesicles 30nm to few microns[9,10]

Advantages
- Enhanced permeation and Passive and non-invasive
- Made from safe and approved materials.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
- Low risk profile.
- Better stability and solubility of many drugs

Disadvantages
- Poor yield.
- Skin irritation or dermatitis due to exipients and enhancers of drug delivery systems.
- Loss of product during transfer from organic to water media

Future prospects of ethosomes
- Introduction of ethosomes has intiated new area in transdermal drug delivery.
- Further reserach in this area will allow better control over drug release *In-vivo* allowing physicians to make therapy more efficient.
- Special emphasis given to skin delivery of Proteins, other Macromolecules, Transcutaneous immunization.

Therapeutic application of ethosomes
- Delivery of Anti-Viral drugs – Acyclovir
- Delivery of Antibiotics - Erythromycin
- Transdermal delivery of Insulin
- Transdermal delivery of Hormonal Agents-Testosterone. Topical Delivery of DNA

Skin infection

A skin infection is an infection of the skin in humans and other animals, that can also affect the associated soft tissues such as loose connective tissue and mucous membranes. They comprise a category of infections termed skin and skin structure infections (SSSIs), or skin and soft tissue infections (SSTIs), and acute bacterial SSSIs (ABSSSIs). They are distinguished from dermatitis (inflammation of the skin), although skin infections can result in skin inflammation.
- Atopic Dermatitis
- Contact Dermatitis (including Poison Ivy and Venenata)
- Psoriasis
- Eczema (including Nummular Eczema)
- Neurodermatitis
- Seborrheic Dermatitis
- Lichen Simplex Chronicus (Lichen Planus)

Topical corticosteroids to treat skin infections
- Topical corticosteroids are widely used for treatment of acute and chronic exacerbations of Atopic Dermatitis (AD) due to their potent immunosuppressive, anti-inflammatory and antihistaminic effects
- Its currently available in various conventional formulations such as creams, ointments, lotions and gels.

Desonide
- Desonide (desonide) 0.05% is an anti-inflammatory and anti-pruritic corticosteroid designed for topical use in inflammatory dermatoses.
- Desonide is a prescription topical treatment for redness, swelling, itching, and discomfort of various skin conditions.
- Desonide is widely used in the treatment of various steroid responsive skin diseases. It is commercially available in cream, lotion, ointment, gel and more recently in foam form also
- Although having low potency, several risk factors involving systemic and local side effects have been associated with this drug

- This leads to need for development of novel drug delivery systems which are able to minimize dose dependent corticosteroid side effects.

Drug and excipients profile

Desonide

- Other names: Prednacinolone, Hydroxyprednisolone acetonide,
- Molecular Formula: $C_{24}H_{32}O_6$ Molecular Weight: 416.514 g.mol-1 Storage: -20°C.

Medical uses

Desonide is a prescription topical treatment for redness, swelling, itching, and discomfort of various skin conditions.

Phospholipid profile

- Phosphatidyl Choline (Lecithin Soya)
- It acts as a wetting, stabilizing agent and good dispersing agent.

Polymer profile

- Hydroxy Propyl Methyl Cellulose (HPMC)
- It is used as thickening agent, binder, film former and hydrophilic matrix.

Ethanol profile

- Ethanol (CH_3CH_2OH)
- It is used as a topical agent to prevent skin infections, in pharmaceutical preparations.

Experimental methodolgy

Calibration curve of desonide

- The standard stock solutions were scanned at wavelengths between 200 and 400 mm for the determination of λ max. The λmax for Desonide was found to be 243 nm.
- The absorbance of these solutions were measured against a blank of PBS pH 7.2 solution in UV/Visible spectrophotometer at 243 nm for Desonide. Standard graphs were then plotted.

Table 1: Calibration data of Desonide in PBS pH 7.2 at 242.5 nm

Concentration (µg /ml)	Absorbance
0	0
20	0.0697
40	0.1381
60	0.2103
80	0.2795
100	0.3508
120	0.4224

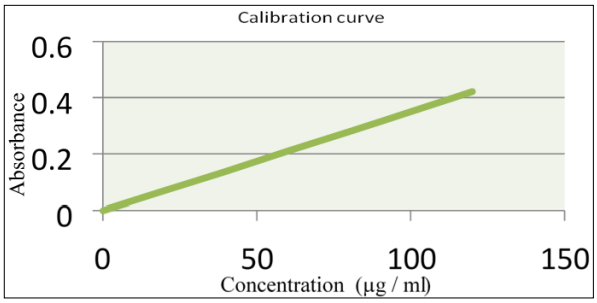

Fig 2: Standard plot of Desonide in PBS pH 7.2 at 242.5 nm

Methodology

Method of preparation of desonide ethosomal vesicles

1. The ethosomal systems investigated here were composed of
   - 1-2% w/v soybean phosphatidyl choline (Lecithin soya),
   - 10–30% v/v ethanol,
   - 0.5% w/v Desonide
   - water to 100% v/v
2. Phospholipid and drug were dissolved in ethanol.
3. Distilled water was added slowly with constant mixing at 500±15 rpm on magnetic stirrer in a container
4. Mixing was continued for an additional 15 mins.
5. The system was maintained at 30°±2°C throughout the preparation
6. The final ethosomal Vesicles were stored at 4°C.

Table 2: Composition of Desonide Loaded Ethosome Formulations

Formula Code	Desonide (%)	Lecithin soya (l-A-phosphatidyl Choline)	Ethanol (%)	Propyle Ne Glycol (%)
EF1	0.5	1	10	10
EF2	0.5	1	20	10
EF3	0.5	1	30	10
EF4	0.5	2	10	10
EF5	0.5	2	20	10
EF6	0.5	2	30	10
EF7	0.5	3	10	10
EF8	0.5	3	20	10
EF9	0.5	3	30	10

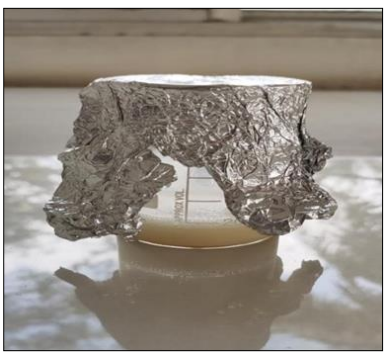

Fig 3: Ethosomal Suspension

Formulation of desonide loaded ethosomal gel

- This optimized EF5 ethosomal suspension was further incorporated into gel
- The aqueous solution of HPMC (1g in 100ml) was Prepared.
- Its was then added to the above mixure stirred until a clear solution was obtained at 300 rpm for sufficient time using a magnetic stirrer followed by adding small drops of tri ethanolamine until sufficiently acceptable consistency of gel was obtained

Fig 4: Desonide Loaded Ethosomal Gel

Results & discussions

Particle size determination

- The particle size distribution along the mean diameter of the all different composition of Ethosomal formulations were measured by using Dynamic Light Scattering Particle Size Analyzer (Malvern instruments).
- Optimized batch of formulation was EF6 which had the highest entrapment efficiency ensuring that the formulation can provide high therapeutic value due to effective dose made available in the system.
- The EF6 formulation contained soybean Phosphatidyl choline shows the least particle size range of 220.1nm among all other ethosomal formulations.

Zeta potential

- All prepared ethosomal formulations were evaluated for its stability study.
- The zeta potential of all formulations were determined by using Zeta meter to measure the vesicle surface charge (zeta potential).
- The zeta potential of EF6 formulation were found to be -1.75 mv**.**

In Vitro Drug Release

- *In Vitro* drug release of Desonide loaded Ethosomal formulations were determined by dialysis diffusion method
- The studies were carried out to ensure the safety, efficacy, product performance, batch to batch uniformity and bioavailability of a drug to produce the desired therapeutic activity
- Hence, in-vitro drug release of all different Ethosomal formulations were analyzed and percentage cumulative drug release were determined.
- The cumulative percentage drug release all 5 formulations were reported in table by taking time in hours on X-axis and cumulative % drug release on Y-axis.

Table 3: Percentage Cumulative Drug Release of Ef1 To Ef9

Time in hours	% Cumulative drug release								
	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8	EF9
0	0	0	0	0	0	0	0	0	0
2	3.02	4.33	5.40	7.50	8.55	9.63	6.8	5.6	3.85
4	20.43	11.85	21.60	24.02	20.97	22.66	23.45	20.6	11.52
6	29.85	25.08	25.61	26.05	28.15	29.22	25.86	23.51	24.65
8	37.35	30.70	35.90	37.70	40.49	41.26	34.5	34.9	30.1
10	45.55	38.9	40.70	42.74	50.15	52.41	40.54	38.4	37.61
24	64.87	77.5	81.70	89.07	93.26	95.56	85.62	80.67	76.54

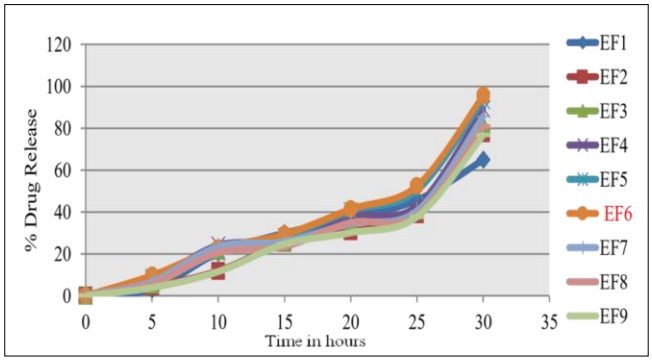

Fig 5: *in Vitro* drug release of ethosomal formulations

Summary & Conclusion

- The research was carried to present the concept Development of nanovesicle based
- Ethosomes incorporation into Gel for the treatment of various skin conditions (Redness, Swelling, Itching, including Psoriasis and Atopic Dermatitis) novel drug delivery carriers are a necessity to deliver the drugs to target site at a faster rate to overcome the drawbacks of multidose therapy, thereby it reduced the frequency of dosing, increased the bioavailability of drug, and increase patient compliance and improve their safety
- The Ethosomes containing topical Corticosteroid (DESONIDE). anti-inflammatory and antipruritic agents were successfully entrapped into the ethosomal vesicles
- During the study different formulations of ethosomes for each drug were developed by varying ethanol concentrations between (10-30%). Concentrations of drug and other excipients were kept constant throughout the study. The particle size distribution of all formulations were in optimum ranges and EF6 showed the least particle range of about
- 220.1 nm and zeta potential rage in -1.2 mv.3
- On conclusion, this formulation produced excellent drug release ensured that this was effective formulation for the treatment of Skin infections. In future, animal studies could be developed to ensure about the exact predictability of effectiveness of the formulation on chronic administration.

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