DESIGN AND EVALUATION OF CHOLINE FENOFIBRATE ETHOSOMAL GEL

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Abstract

The aim of this study was to formulate and evaluate the ethosomal gel of Choline Fenofibrate. Ethosomes is another novel lipid carrier. Ethosomes were reported to improve skin delivery of various drugs. Choline Fenofibrate is a choline salt of Fenofibrate. Choline Fenofibrate is used as Lipid lowering agent for the treatment of hyperlipidemia, hypertriglyceridemia and hypercholesterolemia. The ethosomal system is composed of phospholipid, ethanol and water. Ethosomal system is prepared from soyabeen phosphotidyl choline 2 – 3 % and 20 – 40 % w/w ethanol, drug and water to 100% w/w. The size of optimum ethosomal formulation was performed. It was observed that the formulation (F5) containing **2.5%** of lecithin and **20%** of ethanol showed the particle size of **375.2nm**. After confirm existence of vesicles and their size, drug entrapped by vesicular system was evaluated by ultracentrifugation. While comparing the entrapment efficiency, ethosomes containing 20% w/w ethanol showed highest value with respect to other formulations. The drug release for F5 formulation was found to be highest among all formulations containing 20 % w/w ethanol and 2.5% soy lecithin. Hence it is concluded that F5 formulation containing 20% of ethanol and 2.5% of lecithin was the best formulation for transdermal delivery of Choline Fenofibrate considering all other aspects.

Keywords: Ethosomes, Choline Fenofibrate, soyabeen phosphotidyl choline, hyperlipidemia, hypertriglyceridemia and hypercholesterolemia.

Introduction

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery.

Transdermal drug delivery is a noninvasive technique and can be exploited to circumvent the variables, which could influence the oral absorption of drugs such as pH, food intake and gastrointestinal motility. The greatest challenge with transdermal drug delivery is the barrier nature of skin that restricts the entry of most of the drugs. In dermal and transdermal delivery, the skin is used as a portal of entry for drugs. Because of barrier properties of the outer layer of the skin, in many cases, permeation enhancers are needed to achieve therapeutic concentrations of drug.

ROUTES OF PENETRATION

At the skin, molecules contact cellular debris, microorganisms, sebum and other materials, which negligibly affect permeation. The penetrate has three potential pathways to the viable tissue through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages (Figure 1)

Fractional appendageal area available for transport is only about 0.1% this route usually contributes negligibly to steady state drug flux. The pathway is important for ions and large polar molecules that struggle to cross intact stratum corneum. Appendages may be providing shunts, important at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follicle.

The corneocytes of hydrated keratin comprise of ‘bricks’, embedded in ‘mortar’, composed of multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semi crystalline, gel and liquid crystals domains. Most molecules penetrate through skin via this intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass elegant molecular architecture.

The dermal papillary layer is so rich in capillaries that most penetrates within minutes. Usually, deeper dermal regions do not significantly influence absorption, although they may bind e.g. testosterone, inhibiting its systemic removal.

CARRIER SYSTEMS

Lipid based systems offer excellent candidature for transdermal delivery due to their biocompatibility and ease of mixing with the skin lipids.

Recent approaches in modulating drug delivery through skin have resulted in the design of novel vesicular carriers namely liposomes, niosomes, provesicular systems, elastosomes, deformable liposomes and ethosomes.

Liposomes: Liposomes are lipid vesicles that fully enclose an aqueous Volume.There has been considerable interest on the use of liposomes for transdermal drug delivery. Liposomes are composed of phosphatidyl choline and cholesterol. However conventional liposomes do not offer much value as they cannot penetrate into deeper layers of skin, but rather confined to the upper layer stratum corneum.

Deformable liposomes (Transfersomes): These are the first generation of elastic vesicles introduced by Cevc et al. and were reported to penetrate intact skin carrying therapeutic concentrations of drugs, but only when applied under non occluded conditions. They consist of phospholipids and an edge activator. An edge activator is often a single chain surfactant that destabilizes lipid bilayers of the vesicles and increases deformability of the bilayers. Sodium cholate, Span 80, Tween 80 and dipotassiumglycyrrhizinate were employed as edge activators.

Elastosomes: Bergh (1999) introduced a second generation of elastic vesicles consisting mainly of nonionic surfactants. These surfactant based elastic vesicles were shown to be more effective than rigid vesicles in enhancing skin penetration of various chemical entities.

Ethosomes: It is another novel lipid carrier, recently developed by Touitou et al., showing enhanced skin delivery. The ethosomal system is composed of phospholipid, ethanol and water. Ethosomes were reported to improve skin delivery of various drugs.

MECHANISM OF PENETRATION

Ethanol interacts with lipid molecules in the polar hard group region, resulting in a reducing the rigidity of the stratum corneum lipids, increasing their fluidity. The intercalation of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effect of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier (figure 3)

The drug absorption probably occurs in following two phases:

1. Ethanol effect 2. Ethosomes effect

1. Ethanol effect

Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intercellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.

2. Ethosomes effect

Increased cell membrane lipid fluidity caused by the ethanol ofethosomes results increase d skin permeability. So the ethosomespermeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin

METHODS OF PREPARTION

There are two methods which can use for the formulation and preparation of ethosomes. Both of the methods are very simple and convenient and do not involve any sophisticated instrument or complicated process.

Ethosomes can be formulated by following two methods

Hot method

In this method disperse phospholipid in water by heating in a water bath at 400°C until a colloidal solution is obtained. In aseparate vessel properly mix ethanol and glycol and heat upto 40°C. Add the organic phase into the aqueous phase. Dissolve the drug in water or ethanol depending on its solubility. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.

Cold method

This is most common and widely used method for the ethosomal preparation. Dissolve phospholipid, drug and other lipid materials in ethanol in a covered vessel at room temperature with vigorous stirring add propylene glycol or other polyol during stirring. Heat upto 300°C in a water bath. Heat the water upto 300°C in a separate vessel and add to the mixture and then stir it for 5min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication 6 or extrusion 13 method. Finally, the formulation should be properly stored under refrigeration.

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY

In comparison to other transdermal & dermal delivery systems

- Enhanced permeation of drug through skin for transdermal drug delivery.

- Delivery of large molecules (peptides, protein molecules] is possible.
- It contains non toxic raw material in formulation.
- High patient compliance the ethosomal drug is administrated in semisolid form (gel or cream) hence producing patient compliance.
- Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated Methods.

Materials and Methods

Materials

Choline Fenofibrate was purchased from Hetero drugs pvt. Limited, Hyderabad, India. Potassium dihydrogen phosphate was purchased from Ranbaxy Fine chem.ltd, New Delhi. Soy lecithin, Polypropylene Glycol and Carbopol 934 were purchased from Rolex chemical industries, Mumbai. Ethanol was purchased from SD Fine chemicals. Sodium hydroxide was purchased from Vijayalakshmi enterprises Hyderabad, India

Method

Preparation of ethosomes

Choline fenofibrate ethosomal gel formulation was prepared by soyabeen phosphotidyl choline 2 – 3 % and 20 – 40 % w/w ethanol, drug and water to 100% w/w. For preparation of ethosomes and drug were dissolved in ethanol. Double distilled water was added slowly as a fine stream with constant mixing at 700 rpm in a well sealed container. Mixing was continued for additional 5 minutes. The system was kept at 30°C throughout the preparation and then stored in cool place. The so formed ethosomal system is then incorprated into 1% carbopool gel and pH adjusted using triethyamine.

Evaluation of ethosomal gels

Microscopic examination

Small amounts of the ethosomes derived from ethosomal gel were spread on a glass slide and examined for the vesicles structure and the presence of insoluble drug crystals using optical microscope with varied magnification powers (10× and 40×). Photomicrographs were taken for ethosomes using NIKON digital camera with 3× optical zoom.

pH

The pH measurements of the formulations were carried out using a pH meter by dipping the glass electrode completely into the Ethosomal formulation as to cover the electrode. All the formulations of Ethosomal gels were examined visually for their color consistency and found to appear white,translucent gels without any lumps and aggregates.The pH of all Ethosomal gels was found between 6.0 and 6.9 that lie in the normal pH range of skin, 4.0–6.8 hence the preparations will be irritation-free.

Appearance of ethosomal gels

All developed gels were tested for appearance by visual inspection. They were tested for their appearance and presence of any gritty particles and aggregates.

Entrapment efficiency

The entrapment capacity of Choline fenofibrateethosomes was measured by the ultracentrifuge method.Vesicular preparations containing were kept overnight at 4°C and centrifuged in a ultracentrifuge (Remi) equipped with TLA-45 rotor at 4°C, at 10,000 rpm for 30min. Choline fenofibratewas assayed both in the sediment and in the supernatant. The entrapment capacity of Choline fenofibrate was calculated from the relationship

$$[\frac{T-C}{T}] \times 100$$

Where T is the total amount of Choline fenofibrate that is detected both in the supernatant and sediment, and C is the amount of Choline fenofibrate detected only in the supernatant.

***In vitro* Diffusion Studies**

The *in vitro* skin permeation of Choline fenofibrate from ethosomal formulation was studied using locally fabricated diffusion cell. The *in vitro* diffusion of the drug through semi permeable membrane was performed. The semi permeable membrane soaked in a buffer for 6-8 hours. It was clamped carefully to one end of the hollow glass tube of 17 mm (area 2.011 cm^2) (dialysis cell). This acted as donor compartment. 200 ml of pH 7.4 phosphate buffer was taken in a beaker which was used as a receptor compartment. The known quantity was spread uniformly on the membrane. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37 ± 0.1 ºC. The solutions of the receptor side were stirred by externally driven Teflon-coated magnetic bars at 450 rpm. At predetermined time

intervals, sample was withdrawn and replaced by 5 ml of pH 7.4 phosphate buffer. The drug concentrations in the aliquot were determined at 232 nm against appropriate blank i.e., pH 7.4 Phosphate buffer. This experiment was done in triplicate and average value was reported.

***Ex vivo* permeation studies**

Franz diffusion cell was used for *ex-vivo* permeation studies. Excised rat abdominal skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the ethosomal gel under the test. The receiver compartment contained 25 ml of pH 7.4 phosphate buffer, stirred with a magnetic stirrer at a speed of 450 rpm. The whole assembly was kept on a magnetic stirrer and study was conducted at 37 ± 0.5 ^{0}C. The amount of the permeated drug was determined by removing 2 ml at preset time points up to 24 hrs and replacing with an equal volume of fresh medium. The absorbance was measured at 273 nm spectrophotometrically. The cumulative amount of drug permeated was calculated and plotted against time. Cumulative amounts of drug permeated in µg/cm^2 were calculated and plotted against time. Drug flux (µg/hr/cm^2) at steady state was calculated by taking the slope of the linear portion of the curve. The target flux is calculated using the following equation.

$$\text{Target Flux} = \frac{C_{ss}\ Cl_T BW}{A}$$

FTIR studies (Fourier Transform Infrared Spectroscopy)

Infrared studies were conducted to rule out the interaction between the drug and formulation. Samples are prepared by KBr pellet method and subjected to infrared radiations. The scanning range for FTIR studies was 4000 to 400 cm^{-1}.

Results and discussion

Microscopic examination

A drop of ethosomal gel was sprea on the glass slide and viewed under the microscope. The formed vesicles were spherical in shape. The photograph taken is shown in figure 4.

pH

pH of Ethosomal gel formulations were determined by using pH of all Ethosomal gels was found between 6.0 and 6.9 that lie in the normal pH range of skin, 4.0-6.8 hence the preparations will be irritation free. The of all Ethosomal gels was tabulated in the table 1. The pH of all formulations More or less was equal to the skin pH making the formulations suitable for application on skin aiding in systemic action.

Appearance of ethosomal gels

All the formulations of Ethosomal gels were examined visually for their colour consistency and morphology. Through microscopic observation found to be appear white, translucent gels without any lumps and aggregates. All the formulations of ethosomal gels were examined visually for their colour consistency and found to appear white, translucent gels without any lumps and aggregates (Figure 3)

Entrapment efficiency

The maximum entrapment efficiency of ethosomal vesicles as determined by ultracentrifugation was 54.43 for ethosomal formulation containing 20% ethanol (F5) which was high compared to the formulations containing 30% ethanol (F9-41.80) and 40% ethanol (F11-34.22). Ethanol concentration when taken 20% w/w, there was increase in the entrapment efficiency and with further increase in the ethanol concentration (>20% w/w) the vesicle membrane becomes more permeable that lead to decrease in the entrapment efficiency. Results of entrapment efficiency also suggest that 2.5% phospholipid is optimal concentration for entrapment efficiency also suggest that 2.5% phospholipid is optimal concentration for entrapment efficiency and hence increased or decreased in concentration of phospholipid reduces the entrapment efficiency of vesicles.

Further, when entrapment efficiency was compared different formulations containing same amount of ethanol i.e., 20% formulation containing 3.5% of soy lecithin (F7) was found to show highest entrapment efficiency of 60.53 followed by F6-58.19 containing 3% of soy lecithin. The order of entrapment efficiency of formulations containing different concentrations of soy lecithin

is F7>F6>F5>F4>F3>F2. The order suggests that as the concentration of lecithin increases the entrapment efficiency also increases. Entrapment efficiency of all formulations were tabulated in the table 2.

***In vitro* Diffusion Studies**

- *In vitro* dissolution studies carried out in phosphate buffer of pH 7.4 for 24hrs or till complete exhaustion of the loaded drug from the matrix. In order to find out the order of release and the mechanism, this was predominantly influence the drug release form the matrix.
- Formulation (F5) exhibited highest (71.39) percentage of drug release, which was significantly compared with the plain hydroalcoholic gel (F1-41.56%) and other formulations containing various concentrations of soy lecithin (F2-45.69%, F3-47.98%, F4-56.16%, F6-57.59% and F7-52.95%) and different concentration of ethanol keeping the lecithin concentration constant i.e., 2.5% (F9-41.62% and F11-36.64%) in 24 hr. Further F9 and F11 formulations are compared with the plain hydroalcoholic gels (F8-31.39% and F10-27.56% respectively).
- In the present study it was observed that the drug release rate is increased as the lecithin concentration is increased to 2.5% (F2 to F5), further increase in the lecithin concentration resulted in decrease in release rates (F4 to F6).
- The release rates when compared among the formulations containing varying concentrations of ethanol (F5-20%, F9-30% and F1-40%) keeping the concentrationof lecithin constant i.e., 2.5%, it is observed that F5 formulation containing 20% ethanol showed the highest drug release rates and then F9 followed by F11 (Figure 4, 5,6).
- It suggest that keeping the lecithin concentration of ethanol in increased the release rate are decreased. The release profiles of ethosomal gel of choline fenofibrate (formulation F5, F9 and F11) were shown in the table. The *in vitro* drug release results of formulations (F5, F9 and F11) were fitted into various kinetic models- Zero order, First order, Higuchi model and Peppas model.
- The R2 values of zero order, first order, Higuchi model and Kosmeyer peppas plots of formulations (F5,F9 and F11) ranges from (0.97. 0.86, 0.85), (0.99, 0.90 and 0.88), (0.99, 0.95 and 0.95) and (0.98, 0.93 and 0.93) respectively.

- Further, ethosomal formulations containing different concentrations of ethanol i.e., 20% (F2 to F7), 30% (F9) and 40% (F11) were compared with hydroalcoholic gels of 20%, 30% and 40% respectively (F1, F8 and F10).
- *In vitro* diffusion studies show that ethosomal preparations resulted in high percentage of drug release when compared to the hydroalcoholic gels. The ethosomal containing 2.5% of lecithin and different concentrations of ethanol showed the high drug relase than the respective hydroalcoholic gels. The drug release for F5 is greatee than F1, F9 is greater than F8 and F11 is greater than F10.
- The above results suggest that ethosomal aid in increase in the penetration of the drug into deeper layers of the skin there by showing the systemic action when compared to the plain hydroalcoholic gels.
- The increased penetration when given as ethosomal systems is mainly due to the synergistic action of both ethanol and soya lecithin which makes the vewsicles to travel deeper layer of skin aiding in the systemic action of lecithin and ethanol is not seen the penetration of drug into the skin is less when compared to the ethosomal formulations

***Ex vivo* permeation studies**

After carrying out the *In vitro* diffusion for all the formulations , the best correlation with *In vitro* release. When the study was carried out in rat skin, the formulation F5 (20% ethanol and 2.5% of lecithin) has showed drug diffusion for 24 hrs up to the extent of 78.51% as rat skin has good correlation with *In vitro* release of formulation F5 (Figure 7).

FTIR studies

The major peaks observed in the FTIR of pure drug were 1724, 1641, 1025 and 1079 cm-1 corresponding to the non-hydrogen bonded –C=O stretching C=C aromatic skeletal stretching, C=O=C ether stretch and alcohol C=O stretch respectively. Further, 2885 revealing that the peak contributes C-H aliphatic stretch. Among all observed peaks in pure drug and formulation of ethosomal gel, no significant change in peak wave number will be seen. A few minor changes seen in seen of C-O-C ether stretch and in –C=C- bending vibrations due to the soy lecithin which were found to be in compliance with that reported for pure choline fenofibrate. It can be seen from the IR spectra of formulation (Figure 8).

Conclusion:

Ethosomal formulations containing different concentration of ethanol (20%, 30% and 40%) by varying the concentration of lecithin was prepared the size of best ethosomal formulation was performed. It was observed that the formulation containing 2.5% of lecithin and 20% of ethanol showed the particle size of 375.2nm. Ethosomes containing 20% w/w ethanol showed highest value with respect to other formulations containing 30% and 40% of ethanol. It is concluded that F5 formulation containing 20% of ethanol and 2.5% of lecithin was the best formulation for transdermal delivery ofCholine Fenofibrate considering all other aspects. The highest value of transdermal flux for ethosomes containing 20% w/w ethanol and 2.5% of lecithin is the indication of complete and rapid penetration through the skin may be because of tiny vesicular size.

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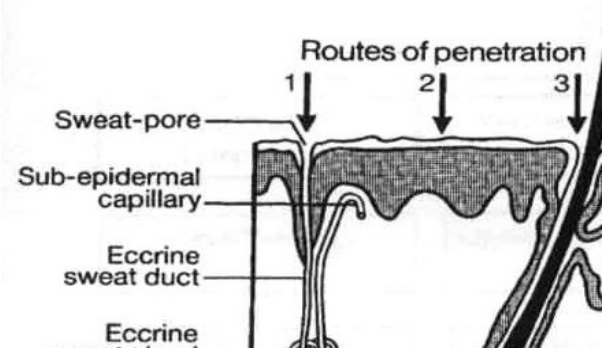

Figure 1: Simplified diagram of skin structure and macroroutes of drug penetration (1) via the sweatducts; (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous glands.

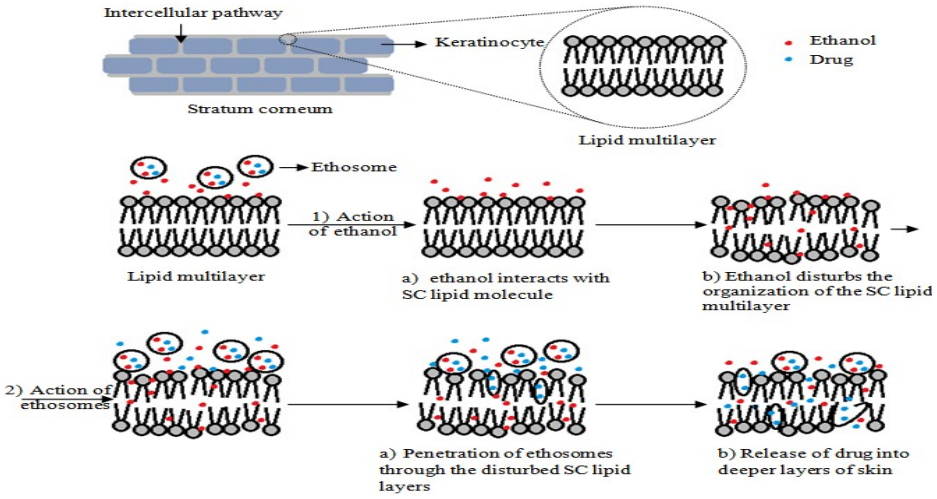

Figure 2: Mechanism of drug penetration

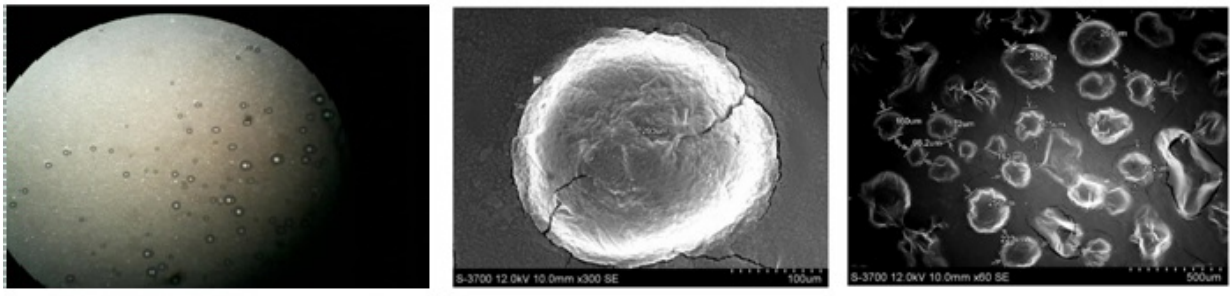

Figure 3: Scanning Electron microscope images

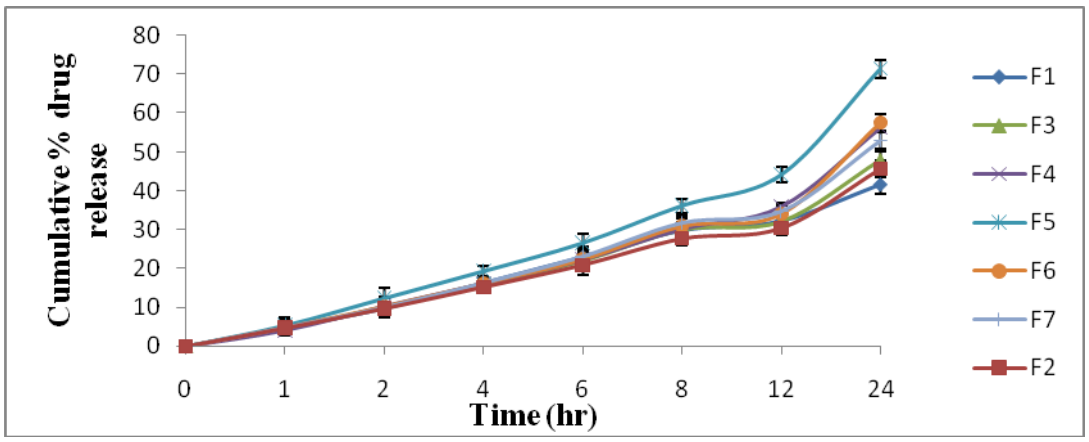

Figure 4: Cumulative drug release profile of formulations containing 20% ethanol (F1-F7)

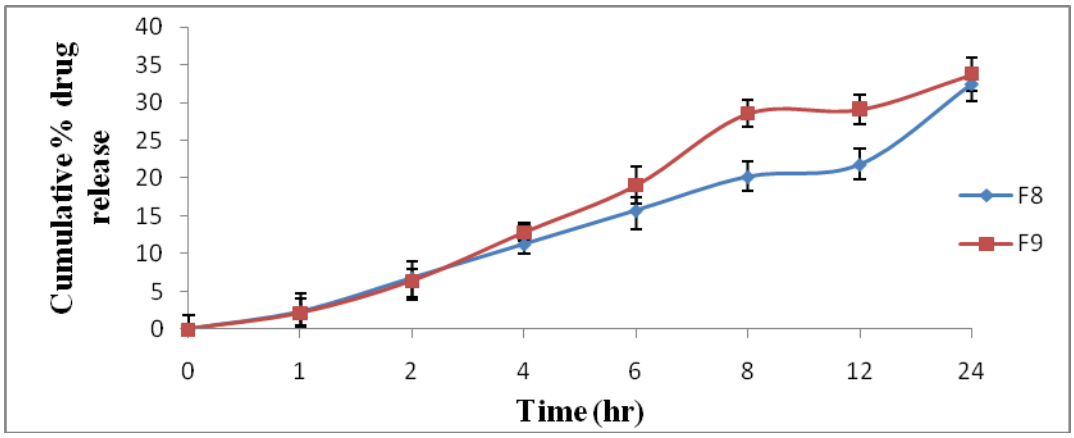

Figure 5: Cumulative drug release profile of formulations containing 30% ethanol (F8,F9)

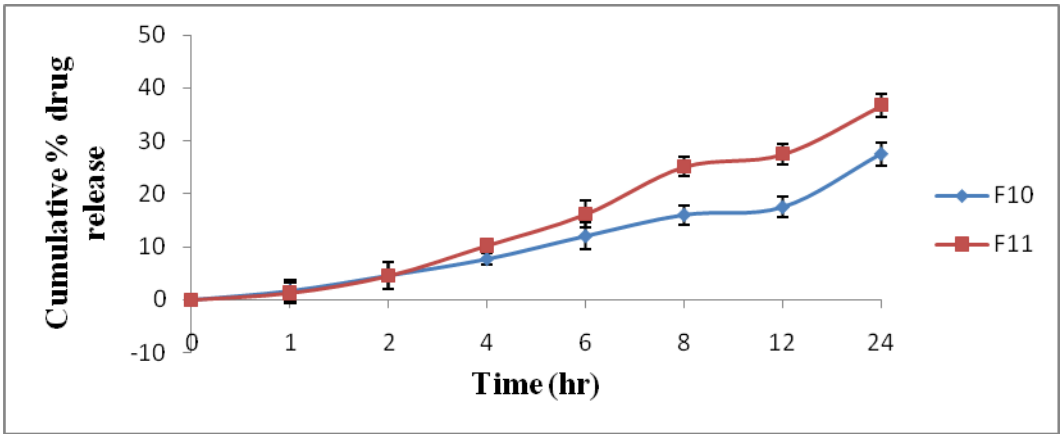

Figure 6: Cumulative drug release profile of formulations containing 40% ethanol (F10, F11)

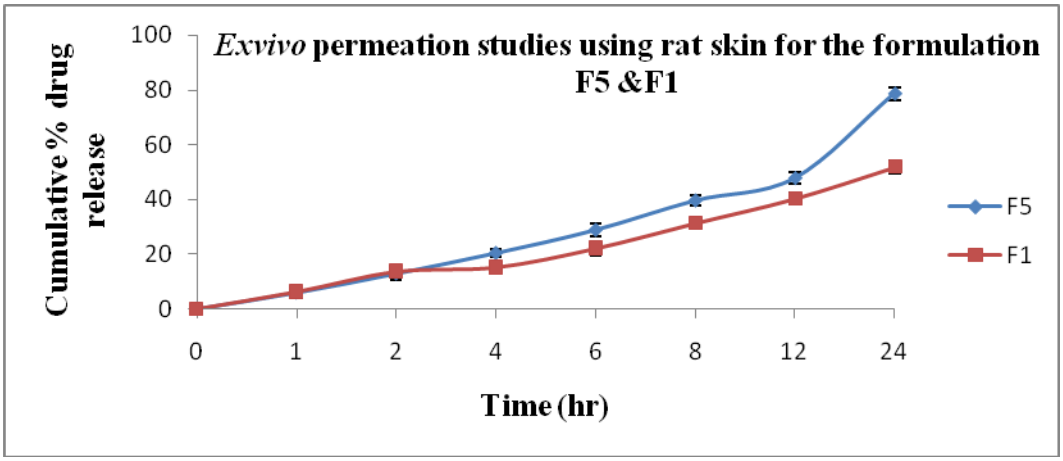

Figure 7: *Ex vivo* permeation studies using rat for the formulation F5 & F1

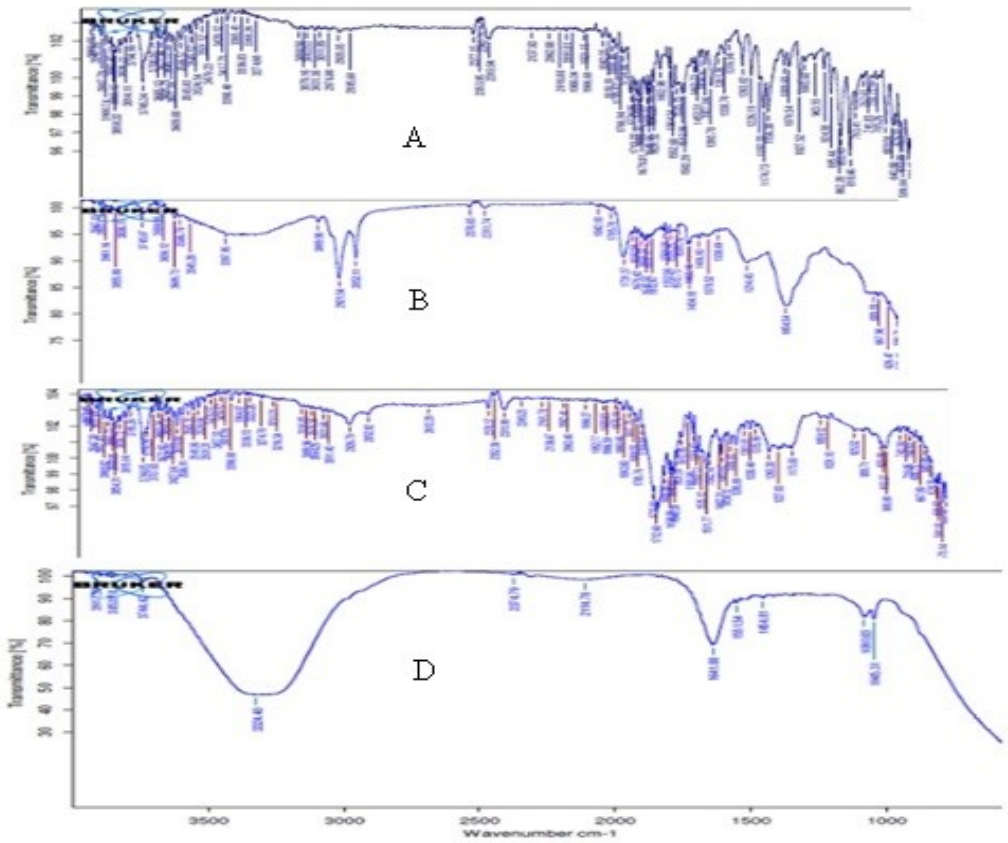

Figure 8: A)IR spectra of choline fenofibrate B) IR spectra of soya lecithinC) IR spectra of carbopol D) IR spectra of Choline Fenofibrate Gel

Table 1: pH of various formulations of ethosomal gels

Formulation code	pH
F1	6.1
F2	6.3
F3	6.2
F4	6.7
F5	6.6
F6	6.9
F7	6.5
F8	6.3
F9	6.8
F10	6.3
F11	6.5

Table 2: Entrapment efficiency of various formulations of ethosomal gels

Formulation code	Entrapment efficiency (%)
F2	18.41
F3	26.73
F4	32.06
F5	54.43
F6	58.19
F7	60.53
F9	41.80
F11	34.22

Table 3: Ethosomal formulation

Formulation code	Composition of materials				
	Drug (mg)	Soya lecithin (mg)	Ethanol (ml)	Propylene glycol(ml)	Water (ml)
F1	100	-	2	1	7
F2	100	100	2	1	7
F3	100	150	2	1	7

F4	100	200	2	1	7
F5	100	250	2	1	7
F6	100	300	2	1	7
F7	100	350	2	1	7
F8	100	-	3	1	6
F9	100	250	3	1	6
F10	100	-	4	1	5
F11	100	250	4	1	5