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FORMULATION AND EVALUATION OF PATCH CONTAINING PRONIOSOMES FOR TRANSDERMAL DELIVERY OF METFORMIN HYDROCHLORIDE

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ABSTRACT

The aim of the present study is to develop transdermal patch loaded with proniosomes that is capable of delivering the entrapped drug over an extended period of time. Metformin HCl, a hydrophilic drug used for the treatment of type 2 diabetes mellitus. Metformin HCl has short half life of 4-6 hrs with oral bioavailability of about 50-60%. Proniosomal TDDS can overcome the permeation barrier of the skin and enhance the permeation of therapeutically active drug molecule. Metformin hydrochloride proniosomes was prepared by coacervation phase separation method using span 40, span 60, cholesterol and soya lecithin. In this study 6 formulations of proniosomes were prepared and their characteristics such as physical appearance, pH, viscosity, particle size, zeta potential, encapsulation efficiency, surface morphology, drug content and *in-vitro* drug release studies were investigated. FT-IR study confirmed the drug-polymer compatibility. Particle size of proniosome was obtained in nanometers. Zeta potential of formulation was found negative indicating the stability of the proniosome. F2 showed higher encapsulation efficiency (87.08 ±0.35) and % CDR (64.22%). Proniosomal formulation F2 was selected and converted into transdermal patches using PVA as backing membrane, HPMC E50 and PVP k30 as rate controlling membrane. Evaluation studies like thickness, weight uniformity, folding endurance, % moisture content, drug content and *in vitro* drug release studies were carried out. The formulation FPT2 showed higher drug content of 17.14 ± 0.32 mg and maximum drug release of 60.58% in 8 hrs. From the data obtained in this study, it was concluded that transdermal patch loaded with proniosomes of Metformin HCl are promising for sustained drug delivery.

KEYWORDS

Metformin hydrochloride, Coacervation phase separation, Proniosomes and Transdermal patch.

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INTRODUCTION

Novel vesicular drug delivery systems have made great progress in the field of nanotechnology. As these systems have a potential to carry a variety of drugs and have been widely used for various purposes, such as drug targeting, controlled release, and permeation enhancement of drug. These

systems are also valuable in evading various drawbacks associated with conventional dosage forms like low aqueous solubility, poor bioavailability, poor membrane permeability, variable plasma concentration, undesirable effects, poor patient compliance and poor patient efficacy. From the last few decades, with various novel drug delivery system approaches including solid lipid nano particles, complexation, electro spraying, solid dispersions, nano emulsion, nano suspension, nano particles had been proposed to resolve these issues[1]. However, too much emphasis was made on vesicular drug carriers, for demonstrating supremacy over conventional dosage forms which involves the encapsulation of drug within vesicles to achieve prolonged effect of drugs and to minimize toxic effects by drug targeting[2]. These systems act as a drug reservoir, can carry both hydrophilic and hydrophobic drug by encapsulation and partitioning in hydrophobic domains and exist in the form of unilamellar or multilamellar spherical structure enclosed by membrane[3]. Advances have been made in the area of vesicular drug delivery, leading to the development of system that allow drug targeting and the sustained or controlled release of conventional medicines[4].

Proniosomes

Proniosomes are either anhydrous free-flowing formulations or liquid crystals with jelly like consistency of water-soluble carrier and they are coated with the suitable surfactants that form niosomes. These can be reconstituted to niosomes with the help of aqueous phase or by hydration in body compartments just before administration. These proniosomal derived niosomes are better than conventional niosomes. Such vesicles do not require specific storage condition and can encapsulate both hydrophilic and hydrophobic drugs[5]. Encapsulation of drug in the vesicular proniosomal structure retains its systemic circulation, provides controlled release, enhances penetration in the targeted area and reduces toxic effects[6]. Stability of Proniosomal preparation is expected to be more stable than a pre-manufactured niosomal formulation. Size distributions of proniosome derived niosomes are better than that of conventional niosomes, resulting in superior release performance[7].

Advantages of proniosomes over niosomes[8-10]

- Proniosomes avoids the stability problems like aggregation, fusion, sedimentation and leaking on storage.
- Avoids hydration of encapsulated drugs which is limiting the shelf life of the dispersion
- Proniosomes are water soluble carrier particles. This has additional convenience of the transportation, distribution and storage.
- Reduce toxicity due to non-ionic nature of surfactant
- Improve penetration and bioavailability of drug
- Both hydrophilic and lipophilic drugs can be formulated as proniosomes.
- Due to depot formation, controlled and sustained release of drugs takes place.
- Biodegradable and biocompatible to the body

Transdermal Patch

Transdermal drug delivery system can be defined as self contained, discrete dosage forms which are also known as patches. When patches are applied to the intact skin, transmits the drug to the systemic circulation via skin at a controlled rate. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across the patient's skin. The main objective of TDDS is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intra patient variation[11]. Transdermal delivery is one of the most effective techniques for drug application. This reduces the load imposed on the digestive tract and liver by oral route. Transdermal delivery will improve bioavailability, enhance duration of action and provide uniform plasma levels. These results in reduced side effects, reduced dosing frequency and improved therapy due to maintenance of plasma levels till the end of the dosing interval when compared to drop in plasma levels with conventional oral dosage forms. Along with

controlled and constant drug administration, transdermal delivery also offer continuous input of drugs having short biological half- life and prevents pulsed entry into systemic circulation[11].

Metformin is most widely prescribed drug for treatment of individuals with type 2 Diabetes mellitus[12]. The drug is currently administered orally in divided multiple doses ranging from 500 to 2,500mg/day[13]. Metformin hydrochloride lowers both basal and postprandial elevated blood glucose in patients with type 2 diabetes[14].

Metformin has short half life of 4-6 hours with oral bioavailability of about 50-60%. Therefore frequent dosing is required but it results in high incidence of gastro intestinal side effects[15]. The most severe side effects of Metformin relates to its association with lactic acidosis. Metformin also cause gastrointestinal side effects, including vomiting, diarrhea, abdominal pain, drowsiness, stomach pain, flatulence and loss of appetite[12].

Thus the development of suitable drug delivery system for Diabetes mellitus, which will maintain a proper blood level for a long period of time without adverse effects connected with frequent oral administration, is very important[15]. Advantage of using proniosomes of Metformin transdermally is its ability to bypass the gastrointestinal system. This allows the drug to not have the gastro intestinal side effects associated with oral Metformin[16]. Proniosomal TDDS can overcome the permeation barrier of the skin and acts as a penetration enhancement of the therapeutically active drug molecule and will show faster onset of action that last for a longer period of time[17,13].

In the present work an attempt was made to formulate and evaluate patch containing proniosomes for transdermal delivery of Metformin hydrochloride in order to eliminate GIT side effects, sustain the drug release and to decrease the dose requirement.

MATERIAL AND METHODS

Materials

Metformin hydrochloride was obtained as a gift sample from Apotex Research Pvt. Ltd. Span 40 and span 60 were obtained from Loba Chemie Pvt. Ltd. Cholesterol, soya lecithin, PVA, HPMC E50, PVP K30 and dibutyl phthalate were obtained from yarrow chem. Other excipients used to prepare proniosomes were of standard pharmaceutical grade.

Pre-formulation study

Preparation of standard calibration curve

For the preparation of standard calibration curve, concentration of 2- 12µg were prepared by pipette out 0.2, 0.4, 0.6, 0.8, 1, 1.2ml of the 100µg/ml solution into a 10ml volumetric flask and make up the volume with buffer. The absorbance of each solution was measured at absorption maxima using UV-visible Spectrophotometer[18].

Drug excipients compatibility study

The drug - excipients compatibility studies were performed in order to confirm absence of any interaction between drug and excipients. FT-IR spectroscopy was employed to ascertain the compatibility between drug and selected polymer. The IR spectrum of pure drug (Metformin HCl), physical mixture of drug and polymers were recorded by FTIR spectrometer. FTIR spectra of the drug with polymers were compared with the standard FTIR spectrum of pure drug[19].

Method of Preparation

Proniosomes were prepared by coacervation phase separation method. Weighed amount of drug, surfactant, soya lecithin and cholesterol were taken in wide mouth glass tube and ethanol was added to it. Open end of the glass tube was covered with lid and warmed in water bath at 60-70□. Aqueous solution was added. Mixture was further warmed. The mixture was allowed to cool at room temperature, until the dispersion was converted to proniosomal gel[15].

Preparation of transdermal patch containing proniosomes

4gm of PVA was dissolved in 100ml water and the solution was poured on to the mould wrapped with aluminium foil and dried at 60□ for 6 hours in an oven. Weigh 300mg of HPMC E50 and PVP k30 and dissolved in 5ml of methanol and 5ml of dichloromethane. Use Dibutyl phthalate as a

plasticizer. Prepared proniosomes was dissolved in above solution and stir it slowly with magnetic stirrer. Cast this dispersion on PVA backing membrane which is casted earlier and dry it. After drying, patches were removed from the mould, wrapped with aluminium foil and keep it in a desiccator[20].

CHARACTERIZATION OF PRONIOSOMAL GEL

Entrapment efficiency

The entrapment efficiency was determined by centrifugation method. Proniosomes was dispersed in 10ml of phosphate buffer of pH 6.8 and aqueous solution was sonicated for 10 minutes. Obtained proniosomal dispersion was centrifuged at 25,000rpm for 30min at 20□. The supernatant was collected and properly diluted using buffer and assayed spectrophotometrically at λ max[21].

The % of drug encapsulation was calculated by following formula

EE% = [(Total drug - free drug) / total drug] * 100

Drug content

The drug content was determined by taking proniosomes in a volumetric flask. They were lysed with ethanol by shaking for 15 minutes, followed by dilution using buffer. Then absorbance was measured against blank at λ max and drug content was calculated[22].

$$\text{Amount of drug} = \frac{\text{Concentration from the standard graph} \times \text{DF}}{1000}$$

Zeta potential and vesicle size analysis

Measurement of zeta potential of the proniosomal formulation was done by using a Malvern nano zeta sizer instrument. The average size and size distribution measurement was carried out by dynamic light scattering with zeta sizer[23].

Scanning electron microscopy

Surface morphology of proniosomes was studied by SEM. A double sided tape that was affixed on aluminium stubs and proniosomes was spread on it. The aluminium stub was placed in vacuum chamber of SEM. The morphological characterization of the samples was observed using a gaseous secondary electron detector[22].

In vitro drug permeation study

The *in vitro* drug release studies were performed using Franz diffusion cell. Cellophane membrane was mounted between the donor and receptor compartment. The weighed amount of proniosomes was placed on one side of the dialysis membrane and the receptor compartment was filled with phosphate buffer of pH 6.8, which is magnetically stirred at 550rpm. At predetermined time interval, samples in the acceptor chamber was removed and placed immediately with equal volume of buffer. After suitable dilution, the sample was analysed spectrophotometrically at 234nm[21].

CHARACTERIZATION OF TRANSDERMAL PATCH CONTAINING PRONIOSOMES

Physical appearance

Transdermal patches were visually inspected for colour, clarity, flexibility and smoothness[24].

Surface pH

A small area of the film was cut out and allowed to swell by keeping it in distilled water for 1 hr in glass tubes. Surface pH was then noted by bringing glass electrodes near the surface[25].

Thickness

The thickness uniformity of the transdermal patch was recorded at three different places using vernier caliper or screw gauge and average thickness was measured[24].

Weight uniformity

Weight uniformity was determined by drying the patch at 60□ for 4 hours before testing. Then it was weighed in digital balance. Weight uniformity was determined by calculating the average weight and weight variation[24].

Folding endurance

Folding endurance was determined by repeatedly folding the patch at the same place till it was broken. The number of times the patches could be folded at the same place without breaking gives the folding endurance value[25].

Percentage moisture content

The prepared patch were weighed individually and kept in desiccator containing silica at room temperature for 24 hours. The patches were

weighed again after specified interval until they show a constant weight. The % moisture content was calculated using following formula[25].

% moisture content = [(Initial weight-Final weight)/Initial weight] *100

Drug content

A measured area of transdermal patch was dissolved in a suitable solvent (PBS 6.8) in specific volume. Then with the help of magnetic bead, the medium was stirred for 5 hours. Then it was filtered using whatman filter paper and filtrate was examined for drug content spectrophotometrically[26].

***In vitro* drug permeation study**

In vitro evaluation of transdermal patch was carried out in Franz diffusion cell. The patch was mounted carefully between the receiver and donor compartment of diffusion cell. During over all experiment temperature was maintained at 37 ± 0.5□ and through receptor compartment sample was withdrawn at predetermined time interval. The same volume of PBS was added to receptor compartment to maintain sink condition and the sample was analysed spectrophotometrically[26].

***In vitro* drug release kinetics**

The dissolution profile of all the batches was fitted to zero order, first order, Higuchi and Peppa's to ascertain the kinetic modeling of the drug release. The results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (Zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (First order rate kinetics)
- Cumulative percentage drug release Vs. √t (Higuchi classical diffusion equation)
- Log of cumulative percentage drug release Vs. Log time (Peppa's exponential equation)[24]

Stability studies

Due to insufficient time, stability study of transdermal Patch was carried out for 2 months, according to the modulated ICH guidelines under the following condition: 40 ± 2□ with 75 ±5% RH. Then the patches were analysed for drug content and drug release[26].

RESULTS AND DISCUSSION

Standard calibration curve of Metformin HCl

Standard curve was prepared at the concentration of 2µg/ml to 12µg/ml in pH 6.8 PBS. Calibration curve is given in the Figure No.1 which gave a linear plot with values 0.014 and 0.999 as slope and R^2 respectively at wavelength 234nm.

Drug excipient compatibility studies by FTIR

The compatibility between drug and polymer was carried out using FTIR peak matching method. All major peaks present in the spectrum of pure drug were observed in the spectrum of drug-polymer mixture. The FTIR of pure drug was characterized by C=N bonding at 3387.71cm^{-1}, C- N bonding at 1166.92cm^{-1}, N-H bonding at 1624.06cm^{-1}.

The FTIR of PVP k30 was characterized by C=N bonding at 3385.78cm^{-1}, C-N bonding at 1082.07cm^{-1}, N-H bonding at 1647.21cm^{-1}.

The FTIR spectra of HPMC E50was characterized by C=N bonding at 3329.14cm^{-1}, C-N bonding at 1083.99cm^{-1}, N-H bonding at 1639.49cm^{-1}. This suggests the absence of any chemical interaction and it is concluded that there was no incompatibility between the drug and polymer. All the characteristic IR peaks related to pure drug Metformin HCl also appeared in the FTIR spectrum of drug mixed with polymer, so there was no chemical incompatibility between drug and polymer.

Entrapment efficiency and drug content

The percentage entrapment efficiency of proniosomal formulations F1-F6 was determined to find the best in terms of entrapment efficiency. The percentage entrapment efficiency was in the range of 60.04% to 87.08% and shown in Table No.3. Higher entrapment efficiency was found in the formulation F2, which may have an optimum cholesterol and surfactant ratio to provide entrapment for Metformin HCl. Very low cholesterol content (F6) was found to cause low % EE (60.04), which might be because of the leakage of the vesicles.

Scanning electron microscopy

The shape and surface morphology of the prepared proniosome were observed by scanning electron microscopy. SEM photograph of F2 formulations

revealed that proniosome formed were spherical in shape with smooth surface.

Particle size and zeta potential

Particle size and zeta potential of the proniosomes was determined using Malvern zeta sizer instrument. The size of F2 proniosomal formulation was found in nano range 248.8nm. And PDI was found to be 0.402. Zeta potential of F2 proniosomal formulation shown negative value. Zeta potential of F2 was found to be -49.2mV.

***In vitro* drug release study**

The *in vitro* drug release studies were carried out using Franz diffusion cell for 8 hrs. Cumulative percentage drug release from formulation F1, F2 and F3 containing span 60 as surfactant along with different concentration of soya lecithin and cholesterol at the end of 8 hrs was found to be 55.47%, 64.22%, 50.21% respectively. Cumulative percentage drug release from formulation F4, F5 and F6 containing span 40 as surfactant along with different concentration of soya lecithin and cholesterol at the end of 8 hrs was found to be 47.98%, 52.84% and 42.67% respectively. The *in vitro* release study revealed that the cumulative percentage release was maximum for the formulation containing span 60 than those prepared with span 40. From the diffusion study it was found that formulation F2 formulated using span 60 showed higher degree of drug release.

EVALUATION OF PRONIOSOMES LOADED TRANSDERMAL PATCHES

Physical appearance and surface pH

The prepared patches were physically evaluated for their properties. Patches were transparent, flexible and the surface was found to be smooth. The pH of the formulations was in the range of 6.78 to 6.80 that suits the skins pH, signifying the skin compatibility.

Thickness, weight uniformity and folding endurance, % moisture content and drug content of transdermal patch

Thickness of transdermal patch was found to be in the range of 0.21 to 0.24. Wight uniformity of the patches was in the range of 0.23 to 0.25. Weight uniformity study showed that there is no significant difference in average weight among two batches indicating that the patches were uniform throughout. The folding endurance values ranged from 99 to 103. Folding endurance test revealed that patches would maintain flexibility without cracking and breaking, therefore there is lesser chance of drug loss. The patch FPT2 shows highest folding endurance. All these observation are mentioned in Table No.4.

Percentage moisture content and drug content of transdermal patch

The percentage moisture content in 2 different patches was found to be in the range of 1.61% to 1.81%. The formulation FPT1 which is fabricated with PVP k30 as rate controlling membrane showed lowest percentage moisture content. The drug content in transdermal patch loaded with proniosomes was found to be in the range of 15.46mg to 17.14mg. Drug content was found to be more in the patch, which is prepared by using HPMC E50.

***In vitro* drug release study of transdermal patch**

The *in vitro* drug release studies were carried out using Franz diffusion cell for a period of 8 hrs. From the diffusion study it was found that formulation FPT2 containing HPMC E50 as rate controlling membrane showed the highest drug permeation of 60.58%. Patch containing HPMC E50 showed more moisture content. As the hydrophilicity increased, the amount of drug released also increased. This may be due to the result of initial rapid dissolution of the hydrophilic polymers when the patch is in the contact with hydrated membrane.

Kinetics study

The kinetics of drug release was evaluated by zero order and first order equation. The mechanism of drug release from the formulation was determined by the diffusion data fitted into different models like Higuchi's model and Peppa's model and regression co-efficient were depicted in Table No.5. The equations used in these models for data fitting are specified in the methodology section. Higuchi's model and Peppa's model 'R^2' and 'n' the diffusion

exponent indicating the mechanism of drug release. Based on the highest regression value, the best fit model for FPT1 and FPT2 was found to be Higuchi model. From these results diffusion mechanism was confirmed.

Stability studies

The stability studies were carried out for FPT1 and FPT2 at 40 ± 2□ with 75 ± 5% RH for two months. The results indicated that the transdermal patch did not show any physical changes during the study period and drug content of formulation FPT1 and FPT2 was found around 14.67mg and 16.56mg respectively at the end of two months. There were no significant differences found in the percentage cumulative drug release after stability study. From the stability studies it was confirmed that transdermal patch loaded with proniosomes are fairly stable at storage condition.

Table No.1: Composition of proniosomes

Formulation	Metformin HCl (gm)	Span 60 (gm)	Span 40 (gm)	Cholesterol (mg)	Soya lecithin (mg)	PBS pH 6.8 (ml)
F1	200	1500	-	200	1500	10
F2	200	1500	-	400	1500	10
F3	200	1500	-	200	750	10
F4	200	-	1500	200	1500	10
F5	200	-	1500	400	1500	10
F6	200	-	1500	200	750	10

Table No.2: Formulation of proniosome loaded transdermal patches

Formulation code	Rate controlling membrane				Backing layer	
	HPMC E50 (mg)	PVP K30 (mg)	DCM: M (ml)	DBT (ml)	PVA (g)	Distilled water(ml)
FPT1	-	300	5:5	0.5	4	100
FPT2	300	-	5:5	0.5	4	100

Table No.3: % entrapment efficiency and drug content of Metformin HCl proniosomes

Formulation code	% entrapment efficiency	Drug content(mg)
F1	79.86±0.14	134.107±0.24
F2	87.08±0.35	181.124±0.18
F3	68.67±0.18	104.392±0.32
F4	66.74±0.28	100.214±0.35
F5	71.35±0.25	121.687±0.12
F6	60.04±0.32	89.232±0.18

Table No.4: Thickness, weight uniformity folding endurance, % moisture content and drug content of transdermal patch

Formulation code	Thickness (mm)	Weight uniformity(g)	Folding endurance	%moisture content	Drug content(mg)
FPT1	0.21 ± 0.24	0.23 ± 0.24	99 ±5.38	1.61%	15.46±0.13
FPT2	0.24 ± 0.17	0.25 ± 0.35	103 ± 2.71	1.81%	17.14±0.32

Table No.5: Kinetics data of proniosome loaded transdermal patch

Formulation code	Zero order	First order	Higuchi matrix	Peppa's plot	
				R^2 value	N value
FPT1	0.957	0.962	0.972	0.951	0.443
FPT2	0.977	0.974	0.984	0.982	0.396

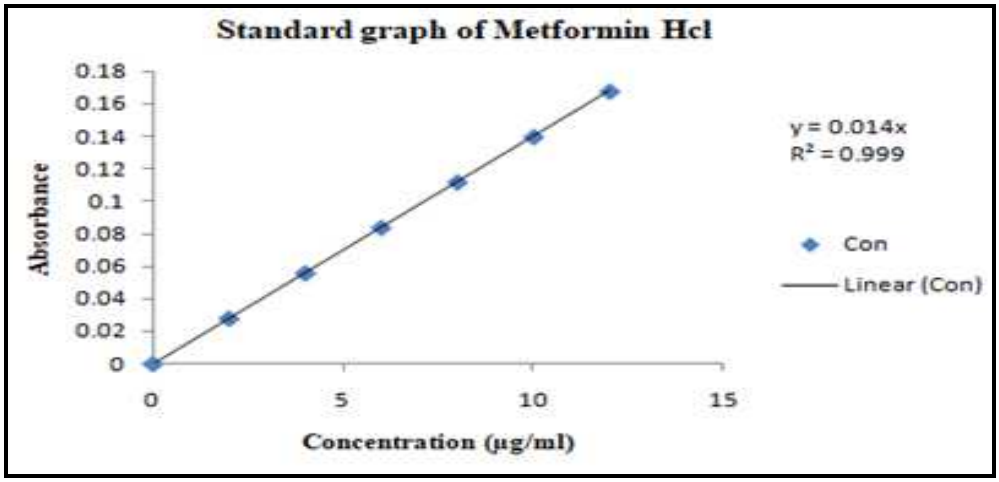

Figure No.1: Standard Plot of Metformin Hcl

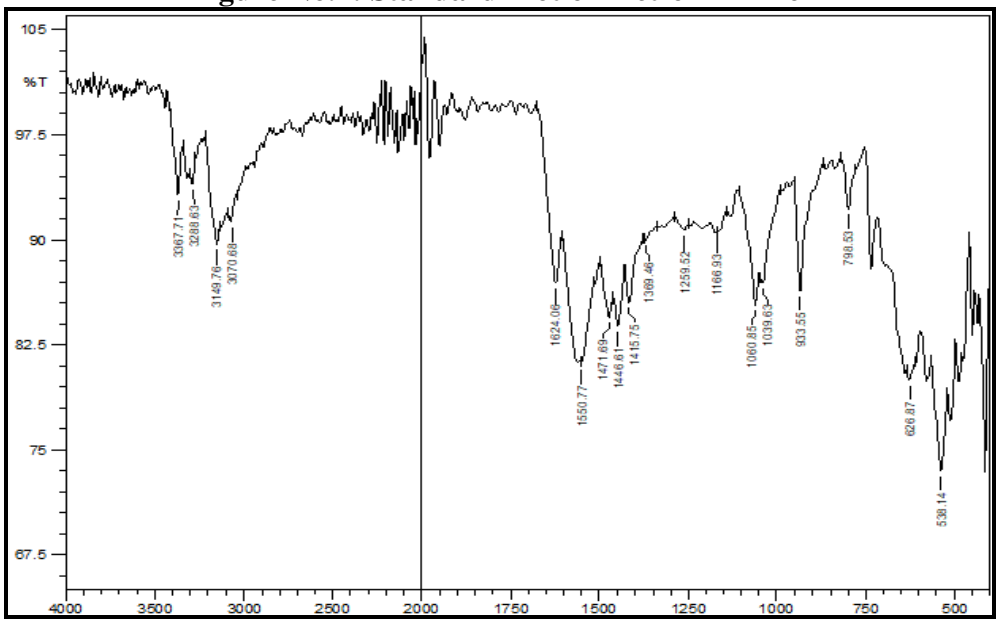

Figure No.2: IR spectra of pure drug Metformin HCl

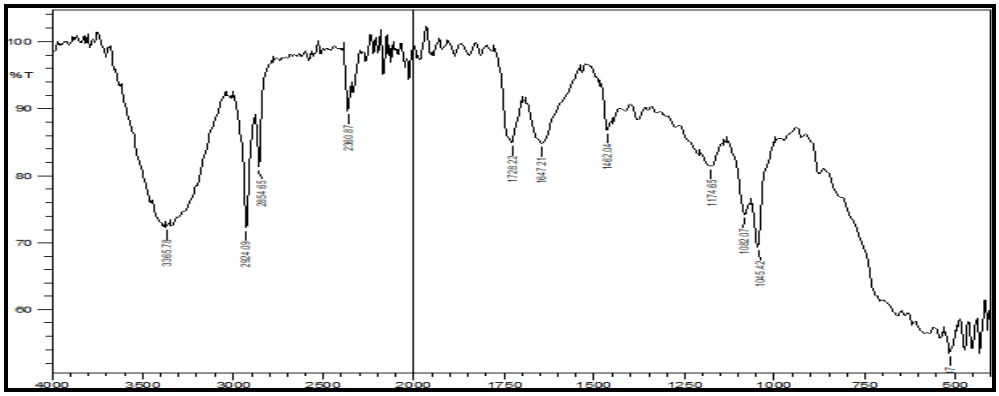

Figure No.3: IR spectra of physical mixture of Metformin HCl with excipients (FPT1)

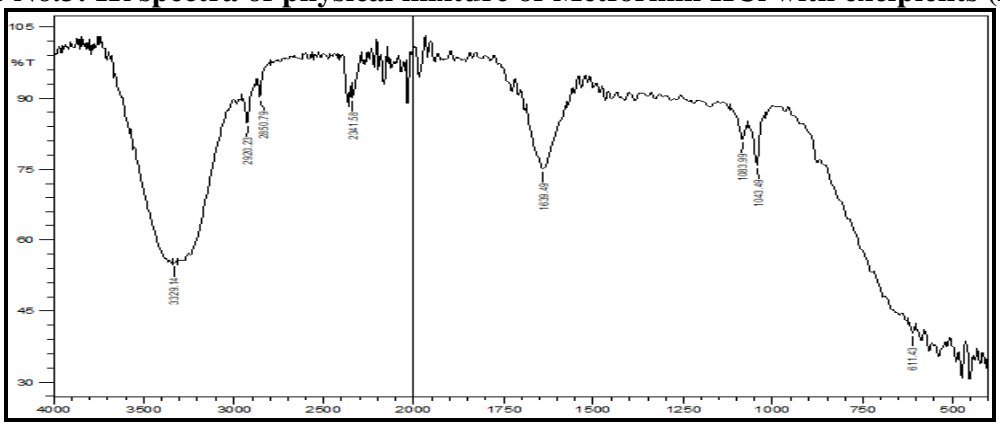

Figure No.4: IR spectra of physical mixture of Metformin HCl with excipients (FPT2)

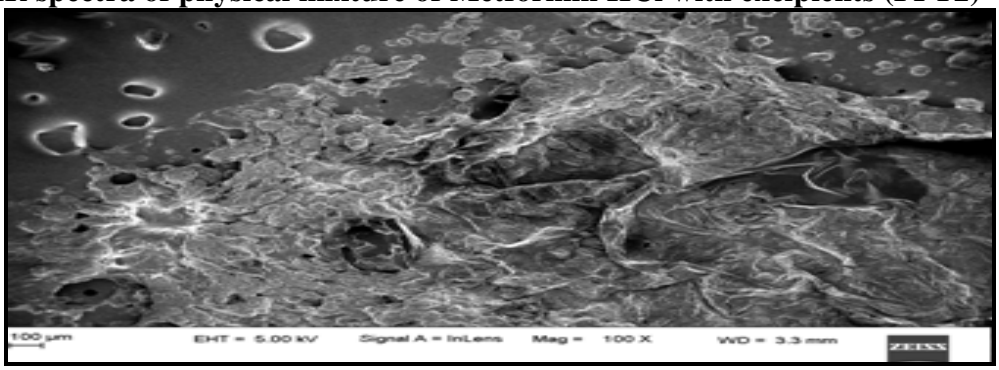

Figure No.5: Surface morphology of F2 proniosome

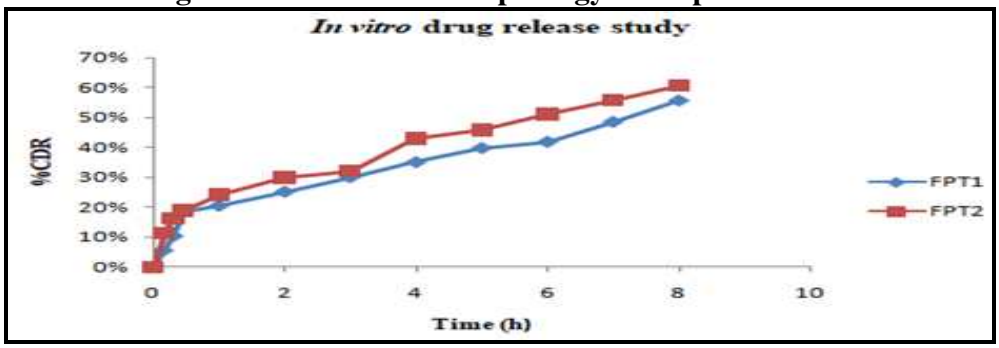

Figure No.6: *In vitro* release profile of FPT1 and FPT2

Higuchi model

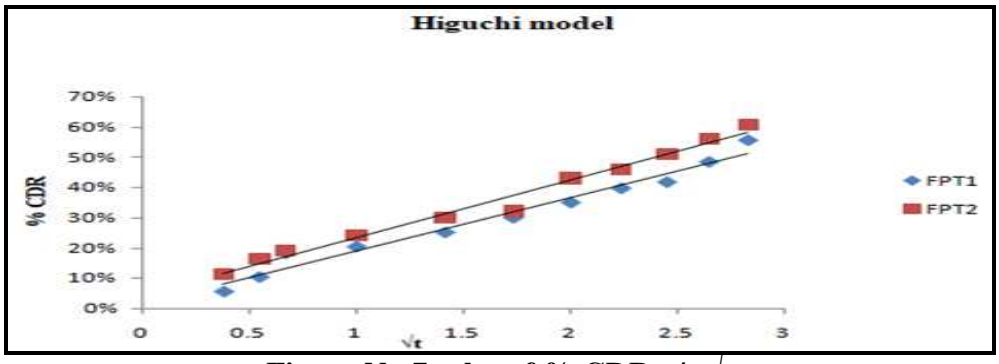

Figure No.7: plot of % CDR v/s √t

CONCLUSION

Transdermal patch loaded with proniosomes of Metformin HCl were prepared successfully using different surfactants span 60 and span 40, soya lecithin cholesterol and two different polymers HPMC E50 and PVP k30.

The following conclusions were drawn from the present investigation

- The FTIR spectral data indicates that there was no interaction between the drug and polymers. All the polymers were compatible with the drug.
- Six proniosomal formulations were prepared by coacervation phase separation method and were evaluated.
- Drug content and entrapment efficiency was found to be more in F2 formulation prepared using span 60 as surfactant. Percentage Alkyl chain length plays a crucial role in percentage EE. As the length of saturated alkyl chain increases, a significant increase in percentage EE was observed. Since the length of saturated alkyl chain of span 60 is more as compared to span 40, proniosomes prepared with span 60 showed higher entrapment.
- Scanning electron microscopy revealed the formation of spherical vesicles.
- Vesicle size of F2 formulation was found in nano range i.e. 248.8nm.
- Zeta potential is important index for the stability of the proniosomal formulation. Zeta potential of F2 proniosomal formulation was found to be negative due to the presence of terminal carboxylic groups in the lipids. Zeta potential of F2 was found to be - 49.2Mv. The high zeta potential increases the repulsion between the vesicles and thus prevents their aggregation and flocculation. So it electrically stabilizes the system.
- From the diffusion study it was found that formulation F2, prepared using 1500mg of span 60, 1500mg of soya lecithin and 400mg of cholesterol shows a large degree of drug release.
- Based on the percentage entrapment efficiency and drug release F2 was selected as best proniosomal formulation and it was converted into transdermal patch using PVA as a backing membrane, PVP k30 and HPMC E50 as rate controlling membrane. Prepared patches were subjected to evaluation parameters like thickness, weight uniformity, folding endurance, percentage moisture content, drug content, diffusion study and stability studies.
- The drug content in the 2 different batches of formulations loaded with proniosomes was found to be in the range of 15.46mg to 17.14mg. Transdermal patch prepared by using HPMC E50 (FPT2) showed highest drug content.
- *In vitro* permeation studies showed that transdermal patch containing HPMC E50 showed larger degree of sustained release.

- Drug release kinetics studies revealed that the release data was best fitted with Higuchi model. The diffusion exponent 'n' value of the Peppa's model was found to be less than 0.45. It shows Fickian diffusion of drug through proniosomal loaded transdermal patch of Metformin HCl.
- Short term stability studies transdermal patches were carried out at 40 ±2□ with 75 ±5 % RH for 2 month. Stability studies showed that there is no significant difference in appearance, drug content and *in vitro* drug release values.
- Results presented in this study suggest that applying proniosomal loaded transdermal patch of Metformin Hcl can achieve sustained drug delivery.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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