IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Development and Evaluation of (ETTS) Externally Triggered Transdermal Therapeutic Systems for Cariprazine by using newly synthesized graft Natural co-polymer- PAAm-g-GGH

Mr. Vijay Sonawane*, Dr. Vishal Babar, Mr. Amit Pondkule , Miss. Madhuri Shikhare, Mr. Ashish Jadhav

ABSTRACT

Cariprazine is an oral antipsychotic approved in the US for the treatment of schizophrenia, acute bipolar mania, and most recently, bipolar depression. The aim of this systematic review is to describe the efficacy, tolerability and safety of cariprazine for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults. Cariprazine in transdermal dosage form would be a lot of fascinating to regulate the mood for extended period by achieving the plasma concentration well higher than the therapeutic levels. With psychiatrical patients, schedules of daily medication should be followed to avoid adverse reactions which are notably difficult. Therefore, delivery of such drugs by transdermal route can be done. Development and maintenance of low dose drugs therapy is desired, which will limit the consequences of significant adverse effect and direct the issues of helpless consistence inthe patients. Ideal quantity of the psychotropic drug can be given by transdermal route with least adverse reactions to overcome the psychic conditions.

In this research work, we have synthesized the novel electrically responsive graft co-polymers using natural polymers with polyacrylamide and utilized for the preparation of cariprazine containing electrically responsive transdermal therapeutic systems (ETTS). The ETTS developed using electrically-responsive graft copolymers of PAAm-g-GGH having crosslinked with glutaraldehyde have confirmed that there was augmented drug permeation under the influence of electric stimuli, while it was reduced without electric current. The Cariprazine permeability got decreased as the concentration of crosslinking agent was increased. Further, higher drug permeability rate observed with increasing electric current strength from 2 to 8 mA. There was a pulsatile pattern of drug permeability under ‘on and ‘off’ electric stimulus mode.

Hence, these graft copolymers are competent biomaterials those could be used for the development of electro-sensitive transdermal therapeutic systems for on-demand drug delivery.

Key words: Cariprazine, Natural Polymers, Polyacrylamide, Drug Delivery

INTRODUCTION

Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist. Doses ≥ 1.5 mg/d yielded 69 – 75% D2/D3 receptor occupancy as measured in positron emission tomography scans. Mean half-life for cariprazine was 2 – 5 d over a dose range of 1.5 – 12.5 mg. Cariprazine produces two clinically relevant metabolites: desmethyl-cariprazine and didesmethyl-cariprazine, the latter having a longer half-life than cariprazine.[1] Exposure to didesmethyl-cariprazine exceeded that of the parent drug. Patients under psychotropic medication can see the inconvenience caused due to side effects due to repeated dosing, for this compliance is of incredible clinical significance. Hence, compliance can be achieved by delivering certain psychotropic drugs through transdermal route. In case of oral administration, GI disturbance like nausea, GI motility and loss of body fluids are observed, therefore this route cannot be safer for psychotropic drugs in the patients who are suffering from peptic ulcer, irritable bowel syndrome and such other conditions, hence transdermal route is the ideal for delivery of such drugs. Thus, it necessary to develop the delivery systems of psychotropic drugs which have lesser side effects and avoid repeated dosing and improve the patient compliance. While treating the disease, delivery of psychotropic drugs can be done by transdermal route which provides better bioavailability with lesser side effects.

Delivery of drugs by transdermal route is more advantageous than oral and parental route; hence it prevents the GI side effects and first pass effect, can attain extended study state concentration of drug in blood and capable to withdraw the drug on removing. Yet, stratum corneum acts as a barrier for this approach.13[2] So, it is important to overcome the stratum corneum while developing the delivery systems of drug by transdermal route; several techniques are utilized to improve the drug permeation through skin.[3] Delivery of drugs by transdermal route can be improved by various non- invasive methods by using chemical enhancers known as chemical method or by using iontophoresis, Sonophoresis, electroporation and magnetophoresis known as physical methods. Delivery of drugs by transdermal route using physical methods with better permeation through skin at required concentration is been reported in several latest studies.[3]

MATERIALS AND METHODS

Materials

Cariprazine was acquired from Gedeon Richter and marketed by Actavis, India. Natural polymer like Gum Ghatti (GGH) and Polyacrylamide, Methanol, Sodium hydroxide (NaOH) Pallets, Potassium dihydrogen ortho phosphate (KH_2PO_4), Sodium dihydrogen ortho phosphate (NaH_2PO_4) were obtained from Hi Media Laboratories Pvt. Ltd., Mumbai. Gum Ghatti (GGH), obtained from Hi Media Laboratories Pvt. Ltd., Mumbai. Ammonium Persulphate (APS) were obtained from Fisher Scientific, Mumbai.

Method

Formulation Studies

Synthesis of electrically responsive graft copolymers

Synthesis of polyacrylamide (PAAm) grafted natural polymers like natural polymer Gum Ghatti (GGH) was done with free-radical polymerization reaction. We soaked about two grams of above said natural polymers in 100 ml double distilled water overnight. The homogenous polymeric solution was heated under atmosphere of nitrogen at 80 ^oC and 0.43 gm of ammonium persulphate (APS) was mixed with polymeric solution and continuously stirred for 20 min to prepare solution;10 ml of 0.105 mol acrylamide was added and polymeric reactionwas carried for 60 min in the atmospheres of nitrogen. The copolymer was cooled at room temperature after 60 min and was poured into excess methanol (400 ml); filtered and fresh methanol was used for washing it repeatedly. Thus, synthesized copolymer wasstored after overnight drying at 50 ^oC. Further, by using below mentioned equations, the grafting parameters were estimated.[4]

Alkaline hydrolysis of graft copolymer

We dissolved two grams of copolymer into 100 ml solution of NaOH (0.9 M). It was stirred continuously for 60 min at 75 ^oC in water bath shaker. After completion of reaction, it was cooled and washed with excess amount of fresh methanol; the obtained product was dried at 50 ^oC overnight.

Characterization of grafted copolymers

The synthesized graft copolymers were characterized by; a) FTIR spectroscopy, b) Elemental (C, H & N) analysis, c) Determining NE values an d) Thermogravimetric analysis (TGA).

Fourier Transform infrared spectroscopy

FTIR was used to analyze and confirm reactions of native, grafted and hydrolyzed copolymers. Pellets were prepared by crushing the sample with potassium bromide under 600 kg of hydraulic pressure. FTIR instrument (Shimadzu, Japan) was used to take the spectra and scanned in between 500 to 4000 cm^{-1}.

Elemental (C, H & N) analysis

Samples of natural polymer, graft copolymer and partially hydrolyzed copolymers were analyzed to estimate the percent of C, H & N.

Determination of neutralization equivalent values (NE)

Neutralization equivalent is the equivalent weight of acid which can be determined by the titration with standard alkali. Two hundred milligrams of the sample were equilibrated with 0.1 N HCl for 6 h, the excess hydrogen ion concentration was backtitrated with a standard sodium hydroxide solution (0.1 N). Then the equivalent weight ofthe carboxylic acid functional groups was calculated.

Thermogravimetric analysis (TGA)

Thermogravimetric analysis was done on native polymers and PAAm-g- copolymers using micro calorimeter (Diamond TG/DTA, Perkin Elmer, USA) in the temperature range of 40-750 ^{o}C, at heating rate of 10 ^{o}C/min within the atmosphere of argon gas flowing rate at 50 ml/min to maintain inert atmosphere.

Preparation of electrically responsive transdermal therapeutic systems (ETTS)

Hydrogel reservoir

The polyacrylamide grafted copolymers were accurately weighed and dissolvedin double distilled water for preparing the hydrogel reservoirs. To maintain the uniformity of polymeric solution, continuous stirring was done using magnetic stirrer. To the above polymeric solution, weighed quantities of drug along with methyl paraben were added and then various concentrations of glutaraldehyde (GA) and 0.5 ml of 0.1 N HCl were added and stirring was carried out for 30 min. Thus, formulated hydrogelreservoirs were stored in a properly closed container for developing the ETTS.

Rate controlling membranes

To prepare rate controlling membranes (RCMs), mercury substrate method was followed. The native polymers Gum Ghatti (GGH) along with polyvinyl alcohol (PVA) together were dissolved in distilled water in different proportions and stirred to get homogenous polymeric solution. The polyethylene glycol 200 (PEG 200), GA and 0.1N HCl were added to the above solution with continuous stirring. This polymeric solution was poured inside the glass bangle placed over mercury in a petri dish. The water was allowed to evaporate at room temperature left for 24 h. dried films were collected and kept in desiccator for further use. [5] Further, the ETTS were developed by precisely measuring an amount of hydrogel equivalent to 10 mg of drug and putting it on the backing layer; prepared RCMs were placed upon hydrogel reservoir and to avoid leakage from the system, the edges were sealed by applying heat and were stored in a closed container. The composition of ETTS is given in Tables 1

Table 1.Formulation details of PAAm-g-GGH based ETTS

Codes	Hydrogel reservoir					Rate controlling membranes				
	PAAm-g-GGH (%w/v)	Cariprazine (% w/wof polymer)	GA (% w/w of polymer)	0.1N HCL (ml)	Methyl paraben (mg)	Gum Ghatti (% w/v)	Polyvinyl alcohol (% w/v)	Polyethylene glycol 200 (% w/w)	GA (% w/w)	0.1 N HCl (ml)
BGG1	1	20	5	0.5	10	2	2	10	4	0.5
BGG2	2	20	5	0.5	10	2	2	10	4	0.5
BGG3	3	20	5	0.5	10	2	2	10	4	0.5
BGG4	3	20	10	0.5	10	2	2	10	4	0.5
BGG5	3	20	15	0.5	10	2	2	10	4	0.5
BGG6	3	20	20	0.5	10	2	2	10	4	0.5
BGG7	3	20	20	0.5	10	2	2	10	8	0.5
BGG8	3	20	20	0.5	10	2	2	10	12	0.5

Evaluation of hydrogel reservoir

Measurement of pH

The graft copolymer hydrogel reservoirs of PAAm-g-GGH were evaluated for pH using a digital pH meter.

Drug content

The 500 mg of PAAm-g-GGH hydrogel reservoirs were accurately weighed and allowed to soak in 100 ml phosphate buffer of pH 7.4for 24 h. The solution was mildly heated, cooled to room temperature and filtered. The absorbance was recorded using UV spectrophotometer (Shimadzu 1700, Japan) at 315 nm [6].

Evaluation of rate controlling membranes

Thickness

The thickness of RCMs was determined using digital micrometer at various places on the RCM; mean thickness was calculated and recorded. [7]

Water vapor transmission studies

Glass vials were used as transmission cells, which have uniform diameters. The prepared RCM (1 sq.cm) was placed and fixed on the brim of cells which is containing around 1 gm fused calcium chloride. The cells were then weighed and placed in closed desiccator containing 200 ml of saturated potassium chloride solution (Relative humidity of 84%). The cells were taken out and weighed at different time intervals and amount of water vapors transmitted was determined by using following formula [8].

WVT=WL / S ---------- (1)

W = Transmission of water vapor gm,L = Thickness of film in cm,
S = Surface area exposed in square cm.
It indicates grams of water transmitted/hr.sqcm

In-vitro drug permeation from ETTS through rat skin

Healthy albino rats (150 to 200 gm) were selected and the hair from abdominal region of rats was cautiously removed without damaging the skin and then it was excised. Dermal side of excised skin was cleaned properly to which tissues and blood vessels are adhered. The ETTS were placed in contact with stratum corneum and was fixed on the donor compartment of Keshary-Chien diffusion cells using an adhesive. The stirrer speed was set at 100 rpm and temperature was controlled at 32 ºC± 5 ºC. Donor compartment containing carbon cathode was fixed on the receptor compartment containing carbon anode. DC power source was used to regulate the applied the electric current. The collection of samples was done from receptor compartment at different time intervals and drug content was determined using UV spectrophotometer (Shimadzu 1800, Japan) at 315 nm

The experiments of drug permeation were done in the below given conditions; (a)without electrical stimulus (passive diffusion), (b) with electrical stimulus using 2, 4, and8 mA currents, and (c) and turning electrical stimulus on–off using 4 mA current.

RESULTS AND DISCUSSION

Synthesis of electro-responsive PAAm-g-GGH copolymer

The acrylamide was grafted on the structure of GGH by free-radical polymerization reaction using APS as initiator under nitrogen purging, When reaction mixture was heated at 80 ºC, APS breakdown occurs to form sulfate anion free radicals, which removes hydrogen from -OH groups of GGH to generate alkoxy macroradical on GGH. This has initiated the grafting of AAm on the GGH backbone (Scheme 1).The solution of NaOH was used for hydrolysis of PAAm-g-GGH copolymer, where graft copolymer undergoes saponification by transforming –CONH2 groups on the backbone of GGH to –COONa groups. The percent grafting efficiency and percent of acrylamide grafted were found to be 97.18% and 82.89% respectively.[9]

Characterization of PAAm-g-GGH copolymer

The PAAm-g-GGH copolymer was characterized by, FTIR Spectroscopy, TGA, Elemental (C, H & N) analysis, Determination of neutralization equivalent values;

FTIR spectroscopy

The FTIR spectroscopic images shown in (Figure 1) are GGH (A), PAAm-g- GGH (B) and hydrolyzed PAAm-g-GGH (C). In case of GGH, the hydroxyl group stretching vibrations are observed at 3471 cm^{-1}, peak of deformation of carbonyl groups are seen at 1660, peak of C–H stretching of cyclic aldehyde was observed at 2930 cm^{-1}. The peaks of C–O stretching of alcoholic groups is observed at 1035 and 1155 cm^{-1}.While considering the PAAm-g-GGH copolymer, the broad peak at 3460$cm^{-1}$is due to the overlap of bonded –NH stretching vibrations and –OH group stretching. The 1630 and 1460 cm^{-1}peaks are attributed to primary amide groups on the backbone of GGH. Peak appeared at1740 $cm^{-1}$was ascribed to the deformation of carbonyl groups of primary amides and the aliphatic –CH stretching vibrations are seen at 2930 cm^{-1}. Hence, this is the support for grafting reaction. But in case of hydrolyzed PAAm-g-GGH copolymer, peak noted at 3450 $cm^{-1}$was because of –OH groups stretching at 2930 cm^{-1}aliphatic –CH stretching vibrations, peak at 1620 $cm^{-1}$was attributed to the presence of primary amide groups present on the backbone of GGH. The peak observed at 1460 $cm^{-1}$was due to COO^{-} groups. This affirms partial hydrolysis of grafted copolymer [10].

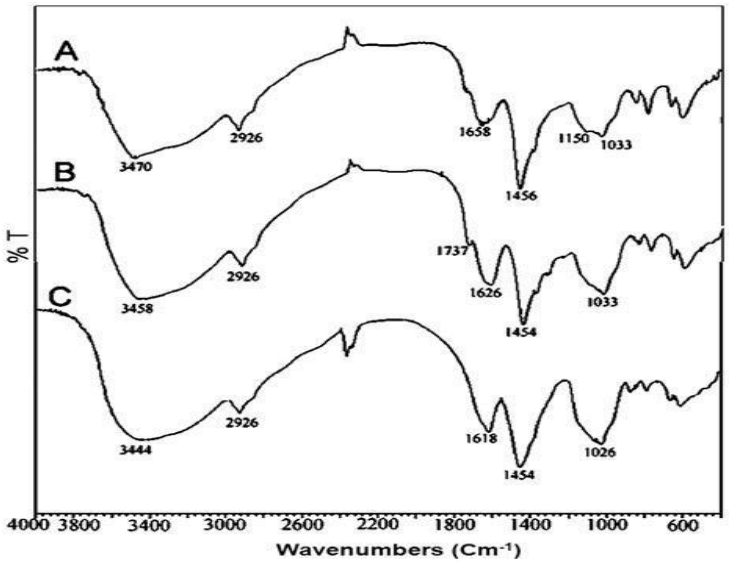

Figure 1.FTIR spectra of GGH (A), PAAm-g-GGH (B), H-PAAm-g-GGH (C) TG Analysis

The TG analysis results for GGH and PAAm-g-GGH can be observed in Figure 2.For GGH, decomposition occurred at 200 ºC; 8.18% mass loss was seen up to 200 ºC because polymer loses its water molecules. The 13.03% of mass loss seen from 200 ºC to 275 ºC; further, a 62.18% of weight loss was observed between 275 ºC and 375 ºC; lastlythe weight loss was reached a value of 65.40% at 400 ºC because of decomposition of GGH. Further, in case of PAAm-g-GGH, the weight loss of 15.17% was observed up to 275 ºC. The weight loss of 55.33% was reported within 275 ºC to 375 ºC and 62.18% weight loss was recorded up to 400 ºC. We observed a constant weight loss in case of PAAm-g-GGH and percent residual mass of PAAm-g-GGH was larger than the un grafted GGH. Therefore, PAAm-g-GGH seems to be more thermally stable than the native GGH. It suggested that the thermal stability of PAAm-g-GGH is better as compared to GGH polymer. It has copious strength and thermal stability since the backbone of GGH was grafted with PAAm. This confirms the formation of graft copolymer comprising GGH and PAAm [11].

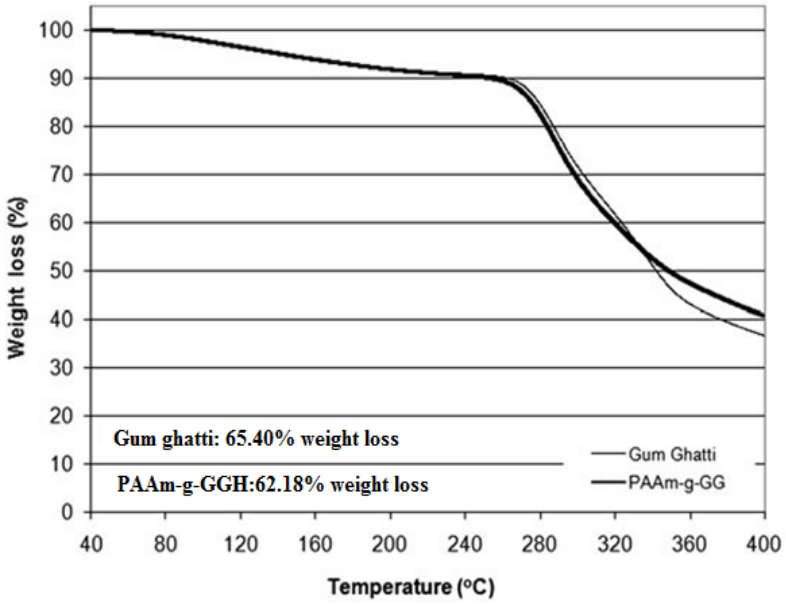

Figure 2.TGA Thermograms of GGH (A) and PAAm-g-GGH (B) copolymer

Elemental analysis(C, H & N analysis)

Elemental analysis results are shown in Table 10. In case of native GGH, it showed 0.79% of N, 38.19% of C and 6.44% of H, wherein case of PAAm-g-GGH; it showed 14.56% of N, 38.26% of C and 6.37% of H. It is observed that after grafting, the PAAm-g-GGH has greater amount of nitrogen, as GGH has –$CONH_2$ groups on its backbone. While, with hydrolyzed PAAm-g-GGH, it showed 4.68% of N, 32.27% of C and

5.90% of H. The reduction of nitrogen content to 4.68% from 14.56% was seen with hydrolyzed PAAm-g-GGH, it is due to fact that the –CONH2groups were transformed to –COOH groups after hydrolysis. Therefore, this confirms grafting and alkaline hydrolysis [12].

Determination of neutralization equivalent values

Neutralization equivalent (NE) values are shown in Table 2. Titration method was used to assess the NE values. The weight of the acid is equal to NE. Upon hydrolysis of grafted polymer, molecular weight remains same, as NH_3 groups are removed and one–OH group is added. As lesser the NE, greater will be the carboxyl groups. The 1673 gm, 1542 gm and 217 gm were the NE values reported for GGH, PAAm-g-GGH and hydrolyzed PAAm-g-GGH. Greater number of –COOH groups were gained by hydrolyzed PAAm-g-GGH than the un grafted GGH. These carboxyl functional groups are accountable for the electrical sensitivity of synthesized PAAm-g-GGH copolymer [12].

Table 2.Elemental analysis and neutralization equivalent measurements of GGH,PAAm-g-GGH and Hydrolyzed PAAm-g-GGH

Polymer	N (%)	C (%)	H (%)	NE
GGH	0.790	38.190	6.447	1673.58
PAAm-g-GGH	14.562	38.265	6.376	1542.63
Hydrolyzed PAAm-g-GGH	4.687	32.275	32.275	217.53

Evaluation of ETTS

Hydrogel reservoir

The prepared hydrogel reservoirs were evaluated for pH and drug content. The reservoirs gel was uniform and translucent; pH was found to be in the range of 6.06 to 7.83, which is in the range of skin and drug content was found in the range of 82.78 to 90.11%, which denotes the proper loading of drug in gel reservoir (Table 3) [12].

Rate controlling membranes

RCMs prepared by using GGH and PVA alone were found brittle and were not useful for developing ETTS, while films formed combination of both GGH and PVA were found thin, flexible and with smooth surface which were suitable for developing ETTS. The film thickness and water vapor transmission (WVT) parameters were used to evaluate the RCMs. 155 to 218µ was the RCM thickness range, which was increased with increasing amount of crosslinking agent. Water vapor transmission (WVT) was determined to understand permeability characteristics of films; it is found that the RCMs were permeable to water vapors. The higher amount of crosslinking agent within the RCMs has affected the WVT rate (Figure 3) [12]

Table 3. Drug content and pH of hydrogel reservoir and thickness of RCM

Formulations	Hydrogel reservoir		Thickness of RCM
	Drug content	pH	
BGG1	84.512	6.06	160
BGG2	82.785	7.83	155
BGG3	86.810	6.56	162
BGG4	88.057	7.66	163
6BGG5	87.823	6.86	165
BGG6	87.577	6.63	165
BGG7	89.070	6.62	217
BGG8	90.810	6.67	228

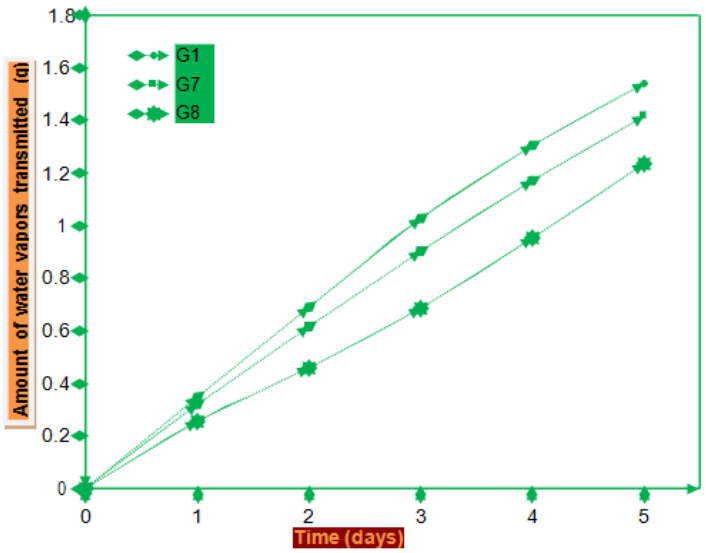

Figure 3. Water vapor transmission profiles of RCMs

In-vitro drug permeation through rat skin

The drug permeation data from all the ETTS with or without DC electric current along with flux values are shown in Figures 4, 5, 6 & 7 and Table 4. Higher amount of drug permeation was observed with the application DC electric current and lesser amount of drug permeation was noted without of DC electric current. Permeation of drug was increased upon enhancing the strength of electric current [12].

Without DC electric current, a 9.41% drug was permeated from the GGH1 formulation which was very small in amount. The drug permeation got decreased with increase in the amount of PAAm-g-GGH copolymer; this is due to higher viscosity of reservoir gel as a result of higher amount of PAAm-g-GGH. On the other hand, drug permeation was affected due to increase in concentration of glutaraldehyde (Figure 4); as concentration of glutaraldehyde was increased, the permeation got decreased. Whereas, application of DC electric current resulted in the increased drug permeation, which shows increased flux values by two

folds; this may be because of the presence of greater concentration of PAAm-g-GGH copolymer in the hydrogel reservoir, which is responsive for the applied electric current (Figure 5 & 7).We observed from the study that the increase in drug permeation relies on formulation variables and application of DC electric current. The drug permeation got decreased when thickness of RCMs was increased. Whereas, the permeation of drug was increased, when strength of the electric current applied was increased from 2 to 8 mA (Figures 6) [13].

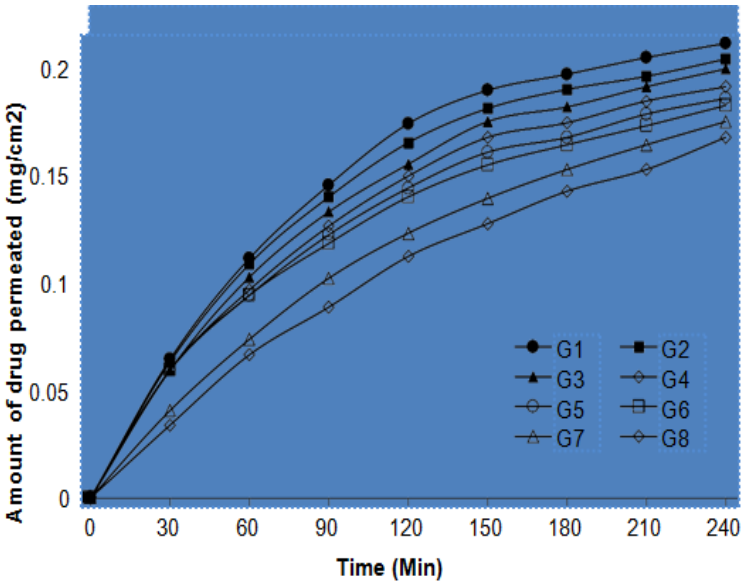

Figure 4.*In vitro* drug permeation profiles of without electric stimulus through ratskin

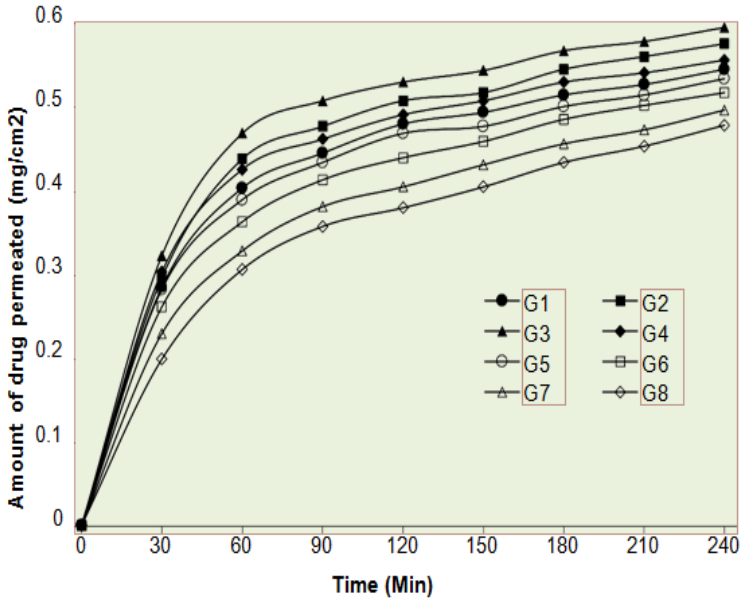

Figure 5.*In vitro* drug permeation profiles with applied electric stimulus throughrat skin

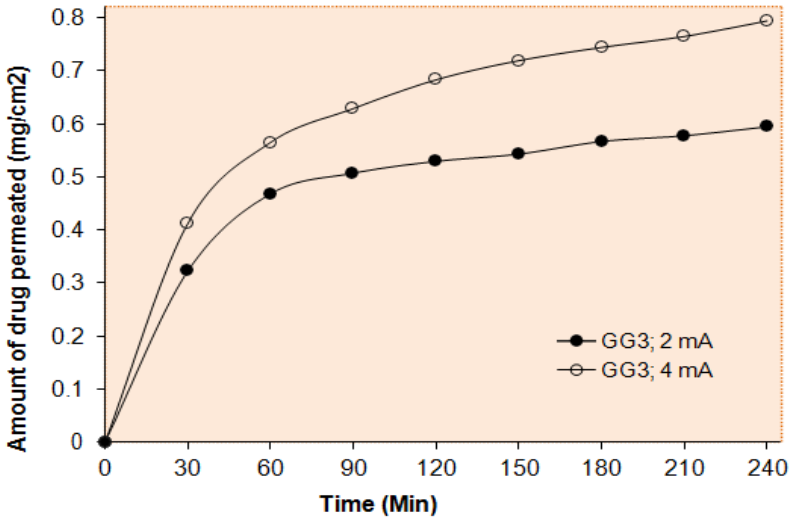

Figure 6. Effect of electric current strength on Cariprazine permeation through rat skin

Table 4. Flux, permeability coefficients, and enhancement factors (*EF*)

Formulations	Without electric stimulus		With electric stimulus		
	Jss ($mg/cm^2/h$)	Pm (mg/hour.cm)	Jss ($mg/cm^2/h$)	Pm (mg/hour.cm)	EF
BGG1	0.0495	0.0125	0.1058	0.0268	2.1368
BGG2	0.0474	0.0120	0.1116	0.0282	2.3531
BGG3	0.0465	0.0118	0.1127	0.0285	2.4181
BGG4	0.0446	0.0113	0.1063	0.0269	2.3796
BGG5	0.0429	0.0108	0.1030	0.0267	2.4015
BGG6	0.0416	0.0105	0.1026	0.0258	2.4620
BGG7	0.0413	0.0107	0.1006	0.0255	2.3786
BGG8	0.0407	0.0103	0.0993	0.0251	2.4375

Jss: Flux ($mg/cm^2/h$), ***Pm***: Permeability coefficient (mg/h.cm), ***EF***: Enhancement factor

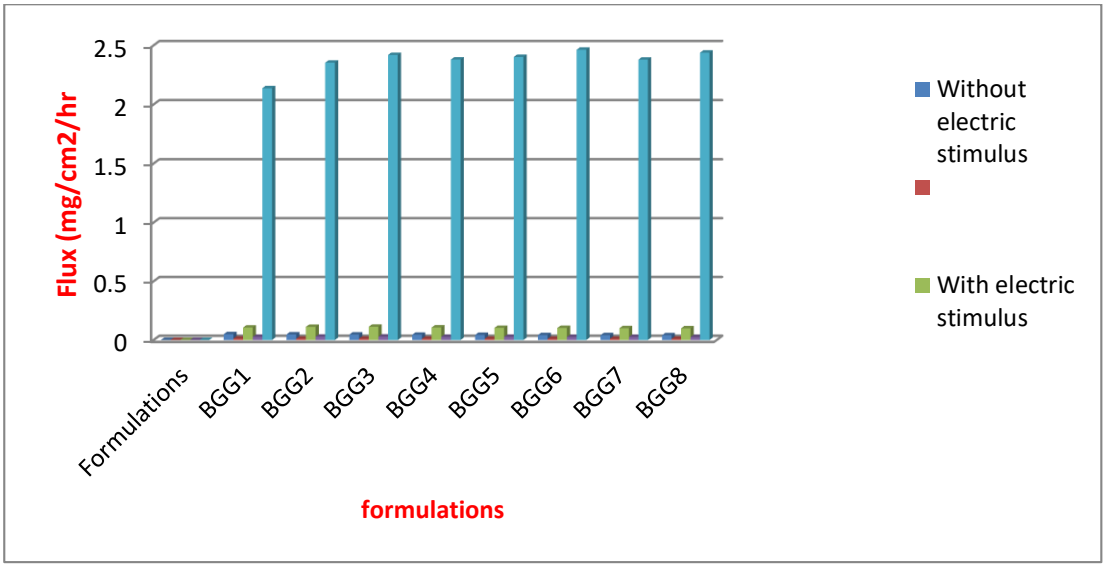

Figure 7. Comparative flux values obtained from drug permeation with and/orwithout electric stimulus

The slope of the linear segment of drug permeation profiles and permeability coefficient (Kp) was used to calculate steady state flux (Jss) using the following equation

$$Kp = Jss/Cv \quad \text{..... (2)}$$

Whereas, CV represents amount of drug present in donor compartment

The below equation was used to estimate the range of enhancement factors (EF), 2.13 and 2.46 is the range reported.

EF = Jss with electric stimulus/Jss without electric stimulus .....(3)

Enhanced permeation of drug was seen after applying DC electric current. Flux values received from developed ETTS in passive & active conditions (with and without DC current) are within 0.0407 to 0.0495 mg/cm^2/h & 0.099 to 0.112 mg/cm^2/h respectively [13]

The Figure 8 represents the drug release behavior of ETTS; permeation rate under "on–off" situation of DC electric current was also reported. Quick permeation of drug was seen when applied DC current was 'on' and permeation of drug was slowed down when applied DC current was 'off' [13]

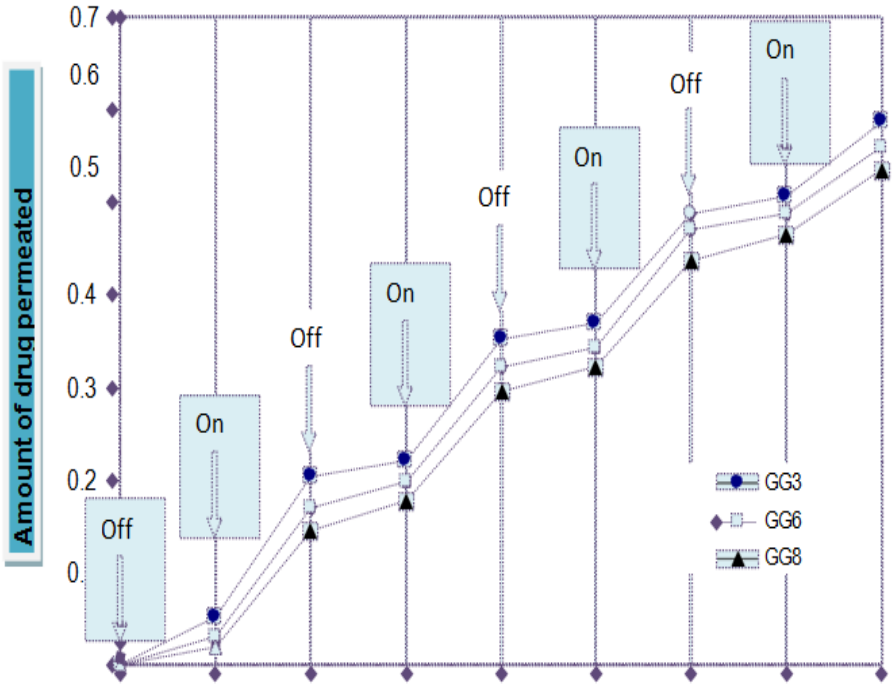

Figure 8. Pulsatile release pattern of ETTS, in which electric stimulus wasswitched on and off at 30 min time intervals

Histopathological evaluation of rat skin

The Figure 9 reveals the change in skin structure after applying DC current. Table 5 shows the scores of changes in skin structure. Intact stratum corneum, much woven structures, no provocative cell penetration or skin extremity changes were seen in the normal skin. We observed the expansion of collagen fiber with minor edema at sub epidermal layer Whereas, with the DC current applied skin, alteration in stratum corneum intactness was seen with loose cell structure, with enhanced cell infiltration in the dermis and erosion of skin appendages. The changes in structure of skin must be the reason of enhanced drug permeation through skin. However, skin without treating with electric current showed slight changes, but the skin treated with electric current showed moderateto marked changes [13]

Table 5.Histopathology of normal skin and skin treated with electric stimulus

Sl. No	Parameters	Normal skin	Skin treated with electric stimulus (4 mA)
01	Stratum corneum intactness	0	3
02	Epidermis liquification	0	4
03	Sub epidermal odema	2	4
04	Collagen fiber swelling	1	4
05	Inflammatory cellinfiltrate	0	3
06	Skin appendages degeneration	0	3

Scores: 0 - No Change, 1 – Very Light Change, 2 – Slight Change, 3 – Moderate Change,4 – Marked Change.

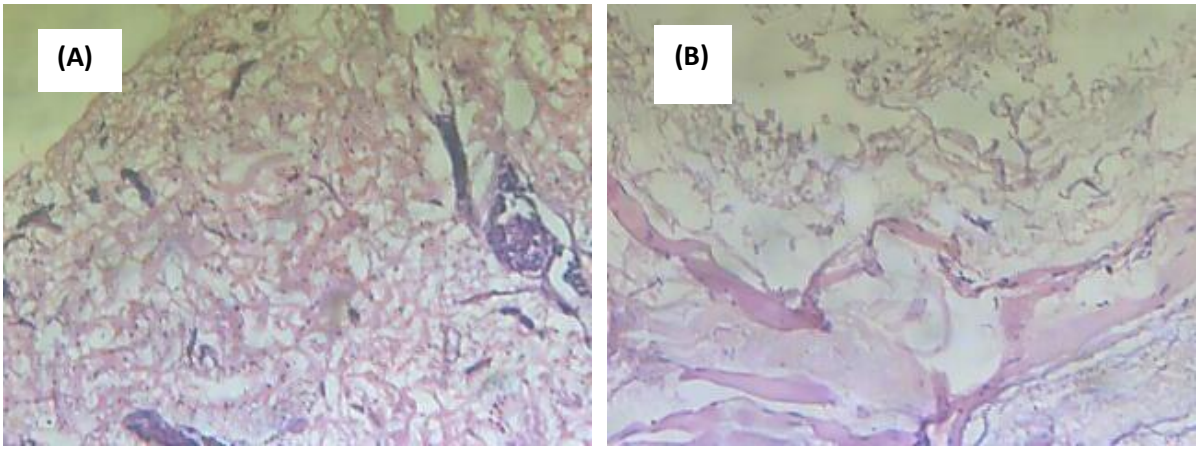

Figure 9.Histopathology of rat skin before electrical stimulus (A) and afterapplication of electrical stimulus (B). (Hematoxylin–Eosin-100)

CONCLUSIONS

We have synthesized the novel electrically responsive graft co-polymer using gum ghatti and polyacrylamide (PAAm-g-GGH) by free radical polymerization method in the nitrogen atmosphere. Further, PAAm-g-GGH copolymer hydrogel was used to develop membrane-controlled ETTS to deliver antipsychotic drug, cariprazine The PAAm-g-GGH copolymer acts as drug reservoir and rate controlling membranes (RCM) were the blend films of crosslinked gum ghatti-poly(vinyl alcohol) and polystyrene film as backing membrane. The pH of the hydrogel reservoir was found in the range of 6.06 to 7.83, while 82.78 to 90.81% was the range of drug content. The thickness of RCMs was measured between 155 to 218 µ and they were permeable to water vapors and rates of WVT were affected by the amount of crosslinking agent. Under passive conditions (without electric stimulus), limited quantity of drug was permeated from the ETTS relying on the various formulations. While, within the vicinity of electric stimulus, the Cariprazine permeation was improved when compared to drug permeation in the absence of electric stimulus the rise in drug permeation by two-fold was seen with utilizing the DC electric current Increased glutaraldehyde amount in RCM and hydrogel reservoir, resulted in the decreased permeation of cariprazine On the other hand, drug permeation rate was enhanced after the applied electrical stimulus was elevated from 2 to 8 mA.

Hence, these graft natural co-polymers are competent biomaterials those could be used for the development of electro-sensitive transdermal therapeutic systems for on-demand drug delivery. These systems also perform like platform technology for incorporation other molecules, which are unable to deliver through traditional transdermal route due to their molecule size, lipophilicity, ionic state etc. and also for those molecules where chronotherapy is essential.

REFERENCE

1. Gyertyán I, Kiss B, Sághy K, Laszy J, Szabó G, Szabados T, Gémesi LI, Pásztor G, Zájer-Balázs M, Kapás M, Csongor ÉÁ. Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochemistry international. 2011 Nov 1;59(6):925-35.
2. Center hf, plaza v. A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, fixed-dose clinical trial evaluating the efficacy, safety and tolerability of cariprazine in patients with bipolar i depression.
3. McIntyre RS, Masand PS, Earley W, Patel M. Cariprazine for the treatment of bipolar mania with mixed features: a post hoc pooled analysis of 3 trials. Journal of Affective Disorders. 2019 Oct 1;257:600-6.
4. Indian Pharmacopoeia-2010, Volume-III, Monographs, Pg. No. 2013-2014.
5. Patil D, Paliwal S, Sharma S, Pattewar S and Singh G. Current Strategies of cariprazine Delivery in Management of Bipolar Disorder and Schizophrenia. J Pharm Sci. Therap, 2019; 5(1): 254-261.
6. Phulzalke S.B, B A Kate, Bagade M. Y, Shete RV. Formulation Developmentand Evaluation of Orodispersible Tablets of Quetiapine Fumarate by SublimationMethod. Asian Journal of Biomedical and Pharmaceutical Sciences, 2016; 6(57): 22-31.
7. Kokate C. K, Purohit A. P, Gokhale S. B. Pharmacognosy. Volume I. Fourty Fifth Edition. Nirali Prakashan .Page no. 7.21-7.22.
8. Anand S. Deshmukh, C. Mallikarjuna Setty, Aravind M. Badiger, K.S. Muralikrishna. Gum ghatti: A promising polysaccharide for pharmaceutical applications. Carbohydrate Polymers. 2012; 87(2): 980-986.
9. K. Sharma, B. S. Kaith, V. Kumar, S. Kalia, V. Kumar, S. Som, H. C. Swart.Gum ghatti based novel electrically conductive biomaterials: A study of conductivity and surface morphology. Express Polymer Letters, 2014; 8(4): 267–281.
10. ChiaraSchiraldi, DonatellaCimini, Mario De Rosa. Production of chondroitin sulfate and chondroitin. Appl Microbiol Biotechnol, 2010; 87:1209–1220.
11. Nicola Volpi. Chondroitin Sulfate Safety and Quality. Molecules, 2019; 24: 1-13.
12. Thiruganesh Ramasamy, Umadevi Subbaih Khandasamy, Suresh Shanmugamb, Himabindhu Ruttalad. Formulation and Evaluation of Chondroitin Sulphate Tablets of Aceclofenac for Colon Targeted Drug Delivery. Iranian Journal of Pharmaceutical Research, 2012; 11 (2): 465-479.
13. Rangari V. Pharmacognosy & Phytochemistry. Volume-I. Third Edition-2012.Chapter-13 Carbohydrates & Related Compounds. Page no. 197-198.