604731

FORM 2

THE PATENT ACT 1970
(39 of 1970)
&
The Patents Rules, 2003
PROVISIONAL/COMPLETE SPECIFICATION
(See section 10 and rule13)

1. TITLE OF THE INVENTION Delivery of nanosized Tiagabine loaded Bio-flexy films using Bio-film former from Solanum lycopersicum biofunctional agent for Oro-soft palatal route

2. APPLICANT (S)
(a) NAME: Prof. (Dr.) N.V. Satheesh Madhav, Dr. Sugandha Varshney
(b) NATIONALITY: Indian
(c) ADDRESS: DIT University, Faculty of Pharmacy, Mussoorie Diversion Road, P.O Bhagwantpur, Makkawala Dehradun (UK) (248009)

3. PREAMBLE TO THE DESCRIPTION

PROVISIONAL	COMPLETE
The following specification describes the invention.	The following specification particularly describes the invention and the manner in which it is to be performed.

4. DESCRIPTION *(Description shall start from next page.)*

5. CLAIMS (not applicable for provisional specification. Claims should start with the preamble — **"I/we claim"** *on separate page)*

Sugandha
Sugandha
2/3/19

6. DATE AND SIGNATURE (to be given at the end of last page of specification)

7. ABSTRACT OF THE INVENTION (to be given along with complete specification on separate page)

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Dehradun (Uttaranchal)

Note: -
*Repeat boxes in case of more than one entry.
*To be signed by the applicant(s) or by authorized registered patent agent.
*Name of the applicant should be given in full, family name in the beginning.
*Complete address of the applicant should be given stating the postal index no./code, state and country.
*Strike out the column which is/are not applicable

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06-Mar-2019/21296/201911008672/Form 2(Title Page)

Delivery of nanosized Tiagabine loaded Bio-flexy films using Bio-film former from Solanum lycopersicum bio-functional agent for Oro Soft Palatal Route

Background of the Invention:

In this work an attempt has been made to explore the potentiality of Soft Palate as novel drug delivery platform for management of epilepsy. Due to drawbacks of conventional oral therapy of dose dumping, increased dose frequency and side effects of drugs, this novel route for drug delivery has been explored. Soft palate is enriched in abundant blood (Middle Meningeal artery, Accessory Meningeal artery, Greater Palatine branch of Maxillary Artery, Ascending Palatine branch of Facial Artery, Ascending pharyngeal artery) and nerve supply (Mandibular branch of trigeminal nerve; Lesser palatine nerve; Greater palatine nerve; Nasopalatine nerve; Glossopharyngeal nerve; Motor nerves).It has Thickness: 158-224μm, pH: 7.34±0.38, Blood flow: 0.89 ml/min/cm^2. Soft palate being part of oral mucosa, acts as smart mucoadhesive site for both systemic and local drug delivery as well as for brain targeting of drugs. It provides controlled, sustained, retentive, systemic as well as site specific drug delivery and leads to enhanced drug bioavailability. Since Trigeminal nerve directly connects from soft palate to brain, thus, when nanosized drug is administered via this route, it directly reaches to brain via inter and intra neural pathways. First Pass metabolism in liver and Pre-systemic

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Dehradun (Uttaranchal)

elimination in gastrointestinal tract gets avoided. Lowest Salivary Secretions, Low Enzyme Activity, avoids acid hydrolysis of drug. Self-medication is possible with proper patient counseling and termination of the drug delivery is achieved by removal of the dosage form from the site.

Tiagabine, anticonvulsant drug, BCS Class **I** Drug **(High Permeability; High Solubility)**.

Tiagabine

IUPAC name: (*R*)-1-[4,4-bis(3-methylthiophen-2-yl)but-3-enyl] piperidine-3-Carboxylic acid

Molecular Formula:$C_{20}H_{25}NO_2S_2$; Molecular Weight:375.55 gm. mol^{-1}

Used for treatment of Infantile Spasms, Focal Seizure, Partial Seizure. Tiagabine Enhances activity of gamma amino butyric acid (GABA), the major inhibitory neurotransmitter in CNS. Blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding on the surfaces of post-synaptic cells. Acts as selective GABA reuptake inhibitor.

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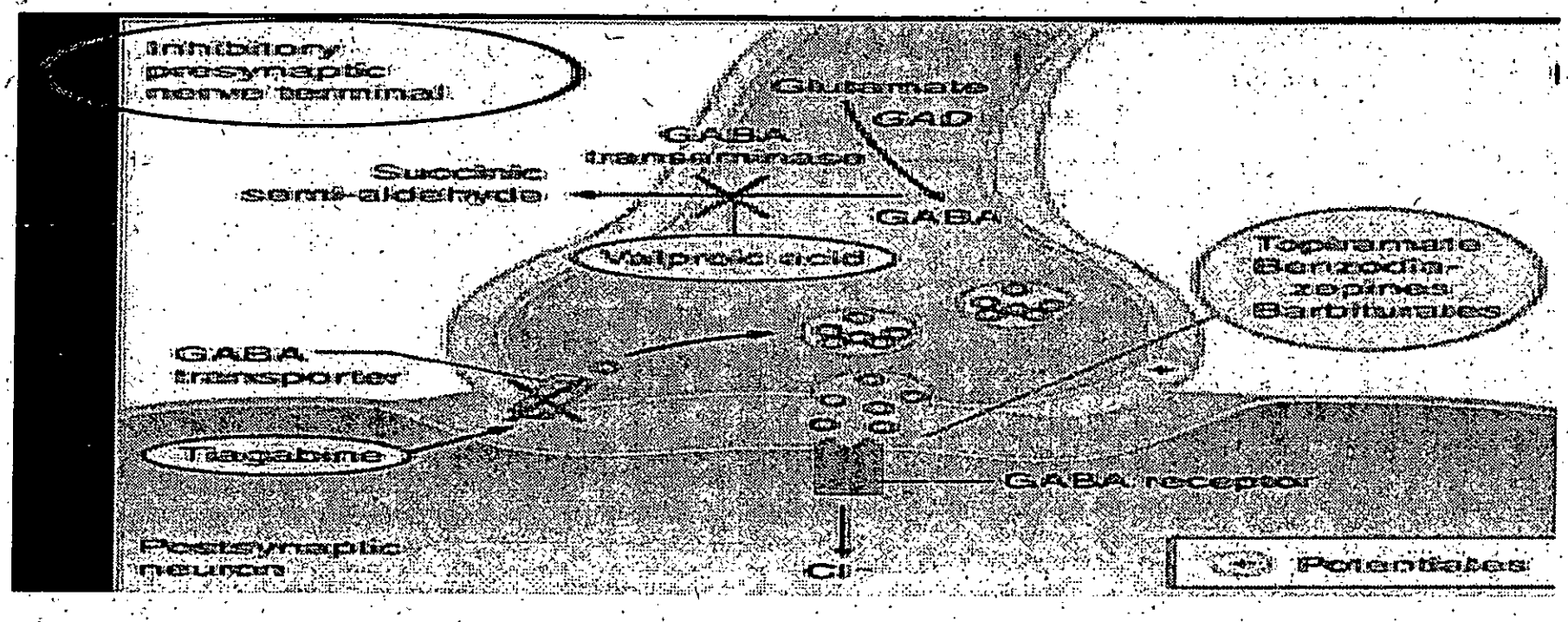
Dehradun (Uttaranchal)



Mechanism of Action of Tiagabine

It possesses plasma $t_{1/2}$: 7-9hours, Bioavailability: : 90-95%, Protein Binding:96%, Renal Clearance:109 ml/min, Plasma Elimination $t_{1/2}$: 7-9 hours, pKa: 3.3, 9.4, Log P:39.3,Onset of Action: 45 minutes,Solubility: Freely Soluble in Methanol, Soluble in aqueous base, Isopropanol, Ethanol, Sparingly Soluble in Water (22mg/ml), Very Slightly Soluble in Chloroform, Insoluble in Non-Polar Solvents. Adverse Effects include abdominal pain, nervousness, insomnia, pruritus, increased appetite, suicidal thoughts and sudden unexpected death.

Tiagabine is available in tablets of 2mg, 4 mg, 12 mg and 16 mg.

In this research work, Novel biopolymer was isolated from pulp of Tomato.It consists of fruits of plant ***Solanum lycopersicum*** belonging to family Solanaceae.Chemical constituents of Solanum lycopersicum includesCarotenoids like Lycopene, Fiber-1.6%, Flavonoids, Naringenin, Quercetin, Vitamins-19.10%

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like Vitamin C, Vitamin B_1, Vitamin B_3, β-Carotene, Malic Acid, Acetic Acid, Formic Acid, Lactic Acid, Fumaric Acid, P-Coumaric, Caffeic, Ferulic and Chlorogenic Acids, **Carbohydrates like Glucose-0.9%, Fructose-1%,Protein-1%, Fat-0.1%**, Minerals like Potassium, Sodium, Calcium, Magnesium, Iron, Zinc. prevents cancer, heart attacks, night blindness and acidosis, strengthen Bones, protects the body from carcinogens produced from cigarette smoke, reduces risk of kidney stones, treatment of GI disorders, lowers Cholesterol levels, Blood Pressure, Protection from Cell Damage, boosts Immunity, reduces migraine, lead toxicity, proper Brain functioning, protects from UV rays, treatment of Vasodilation, Antioxidant, Antidiabetic, Revitalizing Agent, Wound Healing Agent, Humectant.

Biopolymer isolated from Solanum lycopersicum was used as Bio-excipient in formulating nanosized Tiagabine loaded Bio-Flexy Films. Being of natural origin itis biodegradable, bio-safe, biocompatible, non-toxic, non-irritant in nature, non-reactive, and economical than synthetic polymers that are used in marketed pharmaceutical formulations. It possessed mucoadhesive, film former and bioretardant properties.

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D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

Sugandha

Prior Art

Vossler D G *et al.* assessed the side effects and seizure reduction profile of Tiagabine Adverse effects, seizure, and assessment-of data in sequential patients treated open label with Tiagabine were recorded. Behavioral adverse effects occurred in a larger proportion of patients compared to those reported in Tiagabine preapproval randomized controlled trials. Moderate percentage of patients had meaningful reduction in seizure frequency, Tiagabine remains as useful antiepileptic drug.

Kalviainen R reviewed Long-Term Safety of Tiagabine. Short-term safety data of Tiagabine were derived mainly from five placebo-controlled, add-on studies in adults with therapy resistant partial epilepsy, and two conversions to Tiagabine monotherapy studies. Central nervous system (CNS)-related adverse effects, most frequently dizziness, were common with Tiagabine treatment during the titration period; the risk became similar to placebo rates during fixed-dose periods. Other adverse events that were more frequent in Tiagabine- than in placebo-treated patients were asthenia, nervousness, tremor, concentration difficulties, depressive mood, and language problems. Tiagabine doses were titrated slowly and taken with food to avoid rapid increases in plasma concentrations, thus minimizing the risks

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D.I.P. Faculty of Pharmacy
Dehradun (Uttaranchal)

of adverse events. Overall, >2,500 patients have been exposed to Tiagabine during clinical trials, with 1,274 patients treated >12 months, the majority received Tiagabine 24–60 mg/day. No idiosyncratic reactions have been linked to the use of Tiagabine, and no abnormalities in hematology or common chemistry values were reported. No adverse effects on cognitive abilities were detected when the neuropsychological effects of Tiagabine add-on therapy and monotherapy were evaluated. Tiagabine does not appear to cause an excess risk of psychosis or increase the incidence of status epilepticus or spike/wave discharges. No evidence of a relationship between visual field constriction and Tiagabine treatment was found in a study of 15 patients converted to Tiagabine monotherapy (mean dose, 22 mg/day; mean duration, 2.5 years) who had a full ophthalmologic evaluation. The characteristics of Tiagabine in the management of partial epilepsy are enhanced by its favorable side-effect profile in the cognitive area. [51]

Pulman J, Marson AG, Hutton JL2014 suggested Tiagabine as an add-on for Drug-Resistant Partial Epilepsy. To evaluate the effects of add-on treatment with Tiagabine upon seizures, adverse effects, cognition and quality of life for people with drug-resistant localization related seizures. Randomized placebo controlled add-on trials of people of any age with localization related seizures, in which an adequate method of concealment of randomization was used were included. The

studies could be double, single or unblinded and be of parallel or crossover design. Minimum treatment period wasof eight weeks. Trials using an active drug control group were also included. Doses between 30 and 56mg per day are likely to reduce thefrequency of seizures by 50% or more for between 13 and 20% of people.

Wang X, Ratnaraj N, Patsalos P N 2004; revealed the Pharmacokinetic inter-relationship of Tiagabine in blood, Cerebrospinal Fluid and Brain Extracellular Fluid (frontal cortex and hippocampus). Adultmale rats were implanted with either a jugular vein catheter and a cisterna magna catheter for blood and Cerebrospinal Fluidsampling, respectively, or a blood catheter and a microdialysis probe in the hippocampus and frontal cortex (for ECF sampling). Tiagabine was administered intraperitoneally (i.p.) at 20 or 40 mg/kg and blood, Cerebrospinal Fluid and Brain Extracellular Fluid were collected at timed intervals for the measurement of Tiagabine concentrations by high performance liquid chromatography. Tiagabine concentrations in blood and Cerebrospinal Fluidrose linearly and dose-dependently and time to maximum concentration (T_{max}) was 15 and 29 min, respectively. Mean Cerebrospinal Fluid/serum Tiagabine concentration ratios (range, 0.008—0.01) were much smaller than the mean free/total Tiagabine concentration ratios in serum (0.045 ± 0.003). Entry of Tiagabine into Brain Extracellular Fluid (frontal cortex and hippocampus) was rapid with T_{max} values of 31—46 min. Distribution

of Tiagabine in brain was not brain region specific with values in the frontal cortex and hippocampus being indistinguishable. Whilst elimination from Cerebrospinal Fluid was comparable to that of serum, half-life ($t_{1/2}$) values in Brain Extracellular Fluid were three times longer. Tiagabine was associated with linear kinetic characteristics and with rapid brain penetration. Cerebrospinal Fluid concentrations are not reflective of free non-protein-bound concentrations in serum. The observation that Tiagabine elimination from the brain was threefold slower than that was seen in blood, might be due to relatively long duration of action of Tiagabine.

Kalviainen R 2001 reported Long-Term Safety of Tiagabine. Short-term safety data of Tiagabine were derived mainly from five placebo-controlled, add-on studies in adults with therapy resistant partial epilepsy, and two conversions to Tiagabine monotherapy studies. Central nervous system (CNS)-related adverse effects, most frequently dizziness, were common with Tiagabine treatment during the titration period; the risk became similar to placebo rates during fixed-dose periods. Other adverse events that were more frequent in Tiagabine- than in placebo-treated patients were asthenia, nervousness, tremor, concentration difficulties, depressive mood, and language problems. Tiagabine doses were titrated slowly and taken with food to avoid rapid increases in plasma concentrations, thus minimizing the risks of adverse events. Overall, >2,500

patients have been exposed to Tiagabine during clinical trials, with 1,274 patients treated >12 months, the majority received Tiagabine 24–60 mg/day. No idiosyncratic reactions have been linked to the use of Tiagabine, and no abnormalities in hematology or common chemistry values were reported. No adverse effects on cognitive abilities were detected when the neuropsychological effects of Tiagabine add-on therapy and monotherapy were evaluated. Tiagabine does not appear to cause an excess risk of psychosis or increase the incidence of status epilepticus or spike/wave discharges. No evidence of a relationship between visual field constriction and Tiagabine treatment was found in a study of 15 patients converted to Tiagabine monotherapy (mean dose, 22 mg/day; mean duration, 2.5 years) who had a full ophthalmologic evaluation. The characteristics of Tiagabine in the management of partial epilepsy are enhanced by its favorable side-effect profile in the cognitive area.

NANOSIZING OF TIAGABINE

(1)Solvent Evaporation Method: 100 mg Tiagabine mixed with 10 mg dextrose, 5 mg fructose and 10 mL methanol and triturated. Diluted mixture with 50 mL distilled water, sonicated for up to 15 cycles (3mins/cycle) in ultrasonic bath sonicator. Absorbance, % Transmittance, % Blockage (100- %Transmittance) was

noted after every 5 cycles of sonication. After 15th cycle, residue was collected, dried, packed and stored. Non- aqueous solvent (methanol) was used. Solvent was evaporated naturally.

(2) Sonication Method: 100 mg Tiagabine mixed with 10 mg dextrose, 5 mg fructose and 10 mL distilled water and triturated. Diluted mixture with 50 mL distilled water and sonicated up to 15 cycles (3mins/cycle) in ultrasonic bath sonicator. Absorbance, % Transmittance, % Blockage (100- %Transmittance) was noted after every 5 cycles of sonication. After 15th cycle, residue was collected, dried, packed and stored. Aqueous solvent was used.

Similarly Tiagabine was nanosized by Solvent Evaporation and Sonication Methods.

<u>Primarily screening method for nanosized range particles</u>

It is a novel by U.V. Spectroscopy. Transmittance is based on the concept of Tyndall Effect. When light of specified wavelength passes through the media containing particles less than or greater than the specified particle range, the % blockage represents particles beyond the size range whereas the % transmittance is considered that the particles lies above the size range at particular range

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

ISOLATION PROCESS OF *SOLANUM LYCOPERSICUM* BIOPOLYMER:

Procured Tomatoes from local market. Removed outer peel of 500 gm. Tomatoes by immersing in hot water. Pulp + 500 mL of distilled water, slurry obtained filtered using muslin cloth

↓

Filtrate + 1000 mL.propan-2-one (1:2). Refrigeration at 2-8°C for 24 hours, filtered

↓

Centrifuged at 3500 rpm for 15 minutes

↓

Naturally dried obtained biomaterial for 24 hours powdered, passed through Sieve no.120.Optimized six times, calculated % yield and stored in well closed container for further use

CHARACTERIZATION OF SOLANUM LYCOPERSICUM BIOPOLYMER:

1) % yield: 12.4%±0.01
2) Color: Light Red
3) Odour: Characteristic
4) Texture: Powder
5) Solubility: Methanol, partially soluble in water
6) Color Changing Point: 194°C±2
7) Carbohydrates: Present

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8) Spectral Analysis:

(i) Differential Scanning Calorimetry: DSC Peak of **Solanum lycopersicum** biopolymer was obtained at 77.26°C, Peak Height was 1.5747 mW, Delta H was 67.3116 J/g, Onset depicted boiling point at 44.63°C and Glass Transition temperature was 105.90°C.

(ii) Infra-Red Spectroscopy:IR Peaks of **Solanum lycopersicum** biopolymer were obtained at 3161 cm-1, 1618 cm-1, 1942 cm-1, 1398 cm-1, 1165 cm-1, 1844 cm-1 which indicated functional groups RCOOH, RCONH2, C=C-COOH, S=O, RNH2, RCH2OH.

(iii) Nuclear Magnetic Resonance Spectroscopy: 1HNMR Spectra of **Solanum lycopersicum** biopolymer confirmed the presence of carbohydrates residue within the biopolymer extracted as shift of carbohydrate protons were 3-6 ppm and the spectra when compared reflected the peak at 3.5531 ppm.

(iv)Scanning Electron Microscopy: SEM image of **Solanum lycopersicum** biopolymer showed size range of 100 μm, flakes type Irregular structure with smooth texture.

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

CELL-LINE TOXICITY STUDY: Safety of Biopolymer:

MTT cytotoxicity assay

MTT [3-(4, 5–dimethyl thiazol–2–yl)–5–diphenyl tetrazolium bromide] is taken up by the viable cells and reduced to formazan by the "Succinate-tetrazolium reductase" system that belongs to the mitochondrial respiratory chain functioning in metabolically active cells. Formazan formed, is a purple colored water-insoluble product that is largely impermeable to cell membranes, thus resulting in its accumulation within the healthy cells which is solubilized by adding Dimethyl sulphoxide (DMSO). The optical density (OD) of purple colored solution developed was read using a conventional ELISA plate reader at 590nm (maximum absorbance). The ability of cells to reduce MTT provides an indication of the mitochondrial integrity and activity, which, in turn, may be interpreted as a measure of viability and/or cell number.

The ability of the cells to survive a toxic insult has been the basis of most Cytotoxicity assays. This assay is based on the assumption that dead cells or their products do not reduce tetrazolium.

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

Cell-line toxicity data of Solanum lycopersicum biopolymer

Compound ID	Concentration	Absorbance	% Cell Death
Solanum lycopersicum biopolymer	31.25	0.26	-30.9824
	62.25	0.2475	-24.6851
	125	0.248	-24.937
	250	0.206	-3.77834
	500	0.164	17.38035

Cell-line toxicity data of **Solanum lycopersicum** biopolymer in concentrations ranging from 31.25-500 µM revealed **IC50 (µM) of 253.613** and mean % cell viability of almost 100%.Hence isolated **Solanum lycopersicum** biopolymer was

***In-Vitro* Mucoadhesion Study:**

The adhesion strength of the polymer was assessed by Modified Shear Stress Method at different concentrations1%, 2%, 4%, 6%, 8% & 10% of biopolymer. 10% concentration showed maximum mucoadhesivity.

Isolated Solanum lycopersicum biopolymer was used as bio-filming agent in formulating nanosized Tiagabine loaded bio-flexy Films.

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

FORMULATION OF NANOSIZED TIAGABINE LOADED BIO-FLEXY FILMS

FORMULATION Drug: Biopolymer Ratios	FST1 1:0.5	FST2 1:1	FST3 1:3	FST4 1:5	FST5 1:6	FST6 1:10
Tiagabine (mg)	100	100	100	100	100	100
Solanum lycopersicum biopolymer (mg)	50	100	300	500	600	1000
Dextrose (mg)	10	10	10	10	10	10
Fructose (mg)	5	5	5	5	5	5
Glycerine (µl)	10	10	10	10	10	10
Pectin (gm.)	0.6	0.6	0.6	0.6	0.6	0.6
Distilled Water (ml)	20	20	20	20	20	20

Nanosized drug loaded Bio-flexy Films prepared by Solvent Casting Method.Drug: Biopolymers (1:0.5 to 1:10) were mixed to form uniform dispersions, added co-processing agents along with solvent. Subjected to Magnetic Stirring for 15 minutes, followed by sonication for 5 cycles (each cycle 3 minutes).Transferred into petridishes. Kept for natural drying for 24 hours.Prepared Films were removed from petridishesTiagabine was used as Anticonvulsant drug, Glycine max biopolymer as film former, Dextrose, and Fructose as Flexicizers, Glycerine as Plasticizer, Pectin as Film Initiator and Distilled Water as Solvent. Similarly prepared Tiagabine loaded Standard Sodium Carboxyl Methyl Cellulose Flexy Films.

Director
D.I.T. Faculty of Pharmacy
Dehradun (Uttaranchal)

FORMULATION Drug: Biopolymer Ratios	FET1 1:0.5	FET2 1:1	FET3 1:3	FET4 1:5	FET5 1:6	FET6 1:10
Tiagabine (mg)	100	100	100	100	100	100
Sodium Carboxyl Methyl Cellulose (mg)	50	100	300	500	600	1000
Dextrose (mg)	10	10	10	10	10	10
Fructose (mg)	5	5	5	5	5	5
Glycerine (µl)	10	10	10	10	10	10
Pectin (gm.)	0.6	0.6	0.6	0.6	0.6	0.6
Distilled Water (ml)	20	20	20	20	20	20

EVALUATION OF FORMULATED BIO-FLEXY FILMS

Prepared Formulations were evaluated for following parameters:

Thickness, Folding Endurance, Surface pH study, Weight Uniformity Study,Drug Content uniformity, Swelling Percentage Study, Percentage moisture uptake (PMU), *In-Vitro* drug release study (by Modified M .S. apparatus), *Ex-vivo* Studies (Mucoretention and Mucoadhesion Study), *In-Vivo* Study by Sub-cutaneous Pentylene Tetrazole (PTZ) Method, Stability Studies as per ICH Guidelines.

Results: Thickness of nanosized **Tiagabine loaded bio-flexy films containing Solanum lycopersicum biopolymer(FST1-FST6)**Thickness of nanosized **Tiagabine loaded bio-flexy films containing Solanum lycopersicum**

biopolymer (FST1-FST6) was ranging from 0.027±0.003 mm to 0.041±0.002 mm, Folding Endurance: 72-86, Surface pH: 7.01±0.02 to 7.01±0.01, Weight Uniformity: 0.012±0.03 to 0.021±0.02, Drug Content Uniformity: 66.6%±0.35 to 74.8%±0.24, Swelling Percentage: 63%±0.4 to 72%±0.2, Percentage Moisture Uptake (PTU): 2.0%±0.15 to 2.5%±0.12. Mucoadhesion by Dynamic method revealed that Nanosized Tiagabine loaded bio-flexy films containing Solanum lycopersicum biopolymer were mucoadhesive for time period of 30-120 minutes. Mucoretentive Study revealed that Nanosized Tiagabine loaded bio-flexy films containing Solanum lycopersicum biopolymer were mucoretentive for time period of 90-210 minutes. The drug release pattern for formulations **FST1-FST6** containing **Solanum lycopersicum** biopolymer **based on the T50% and T80%** was found to be **FST5 (1:6) > FST4 (1:5) > FST3 (1:3) > FST2 (1:1)> FST1 (1:0.5) > FST6 (1:10)**. In-vitro drug release was performed for all the formulations and the data indicate that drug loaded formulations show the sustained release behavior. Graph was plotted between %CDR and time, the R2 value, T50% and T80% were calculated from graph. Based on all above mentioned evaluation parameters, **FST5** (containing Tiagabine: Solanum lycopersicum biopolymer (1:6)) Bio-flexy film having **R2=0.9363, Peppas Korsemeyer** as best fit model, follows **Fickian Diffusion (Higuchi Matrix)** release mechanism, **T50%: 26 hrs., T80%: 31 hrs.** using BITS Software 1.12. Stability study revealed stable bio-flexy films

Director
D.Y.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

with no significant change in physical appearance and stable pH. Prepared formulations of Tiagabine loaded bio-flexy films containing Solanum lycopersicum biopolymer were suitable for Soft Palatal Delivery.

T50% and T80% values of Tiagabine–Solanum lycopersicum polymer Bio-flexy Films

Ratio	T50 % (hours)	T80 % (hours)
FST1 (1:0.5)	1.46	2.04
FST2 (1:1)	1.68	3.01
FST3 (1:3)	2.21	3.89
FST4 (1:5)	2.60	2.73
FST5 (1:6)	**4.51**	**4.85**
FST6 (1:10)	1.31	2.30

The two-tailed P value was found to be less than 0.05 thus, extremely statistically Significant.

T50% and T80% values of Tiagabine–Sodium Carboxyl Methyl Cellulose Standard polymer Flexy Films

Ratio	T50 % (hours)	T80 % (hours)
FET1 (1:0.5)	39.36	43.82
FET2 (1:1)	39.65	43.30
FET3 (1:3)	9.45	10.49
FET4 (1:5)	7.26	8.12
FET5 (1:6)	**40.66**	**43.79**
FET6 (1:10)	6.67	9.14

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

Kinetic Release of Tiagabine–Solanum lycopersicum polymer Bio-Flexy Films

Release Kinetics Analysis Dynamic Method Formulation of Tiagabine: Solanum lycopersicum Bio-Flexy Films

Formulations	R^2					Best Fit Model	Mechanism of Action
	Zero order	1st order	Higuchi Matrix	Peppas	Hixon Crowell		
FST1 (1:0.5)	0.8080	0.8086	0.8927	0.9138	0.8084	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)
FST2 (1:1)	0.7985	0.7991	0.9162	0.9449	0.7989	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)
FST3 (1:3)	0.8055	0.8063	0.9297	0.9530	0.8060	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)
FST4 (1:5)	0.8317	0.8319	0.9046	0.9049	0.8318	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)
FST5 (1:6)	**0.8454**	**0.8455**	**0.9213**	**0.9363**	**0.8454**	**Peppas Korsmeyer**	**Fickian Diffusion (Higuchi Matrix)**
FST6 (1:10)	0.6784	0.6793	0.9150	0.9277	0.6790	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

Kinetic Release of Tiagabine–Sodium Carboxyl Methyl Cellulose Standard polymer Flexy Films

Release Kinetics Analysis Dynamic Method Formulations of Tiagabine: Sodium CMC Flexy Films							
Formulations	**R^2**					**Best Fit Model**	**Mechanism of Action**
	Zero order	**1st order**	**Higuchi Matrix**	**Peppas**	**Hixon Crowell**		
FET1 (1:0.5)	0.8894	0.8897	0.9356	0.9300	0.8896	Higuchi-Matrix	Anomalous Transport
FET2 (1:1)	0.8852	0.8853	0.9324	0.8424	0.8853	Higuchi-Matrix	Anomalous Transport
FET3 (1:3)	0.8868	0.8868	0.9377	0.9550	0.8868	Peppas Korsmeyer	Anomalous Transport
FET4 (1:5)	0.8906	0.8908	0.9361	0.9514	0.8908	Peppas Korsmeyer	Anomalous Transport
FET5 (1:6)	**0.8360**	**0.8363**	**0.9301**	**0.9084**	**0.8362**	**Higuchi-Matrix**	**Fickian Diffusion (Higuchi Matrix)**
FET6 (1:10)	0.8960	0.8962	0.9372	0.9692	0.8961	Peppas Korsmeyer	Anomalous Transport

Director
D.I.T. Faculty of Pharmacy
Dehradun (Uttaranchal)

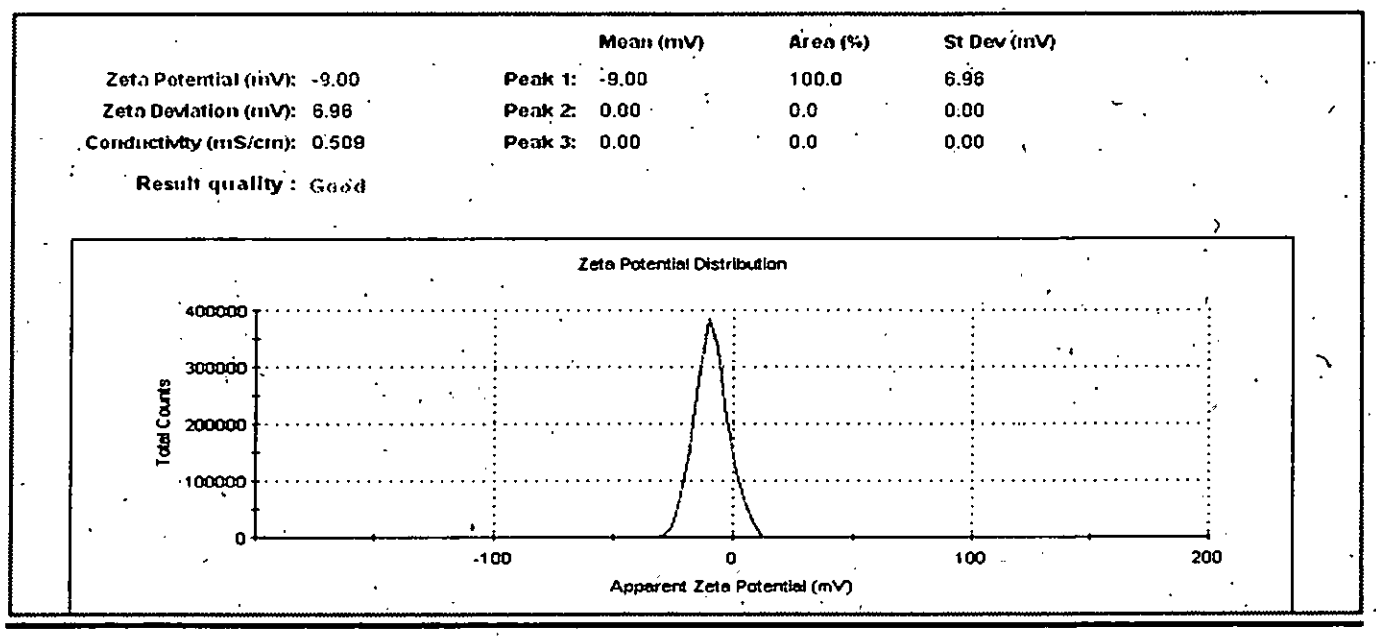
Summary of Invention:

The purpose of this study is to attain brain specificity by delivering nanosized Tiagabine loaded Flexy Films via Oro-Trans Soft Palatal route for Epilepsy treatment. The attempt is made to explore the potentiality of Soft Palatal mucosa as drug delivery platform being enriched with abundant nerve and blood supply, and minimizing side effectes of oral drug delivery. Nanosized Tiagabine loaded bio-flexy films were formulated by Solvent Casting method and evaluated their performance, which depicted their suitability to be administered by Soft-Palatal route.

Director
D.I.P.-Faculty of Pharmacy
Dehradun (Uttaranchal)

DRAWINGS

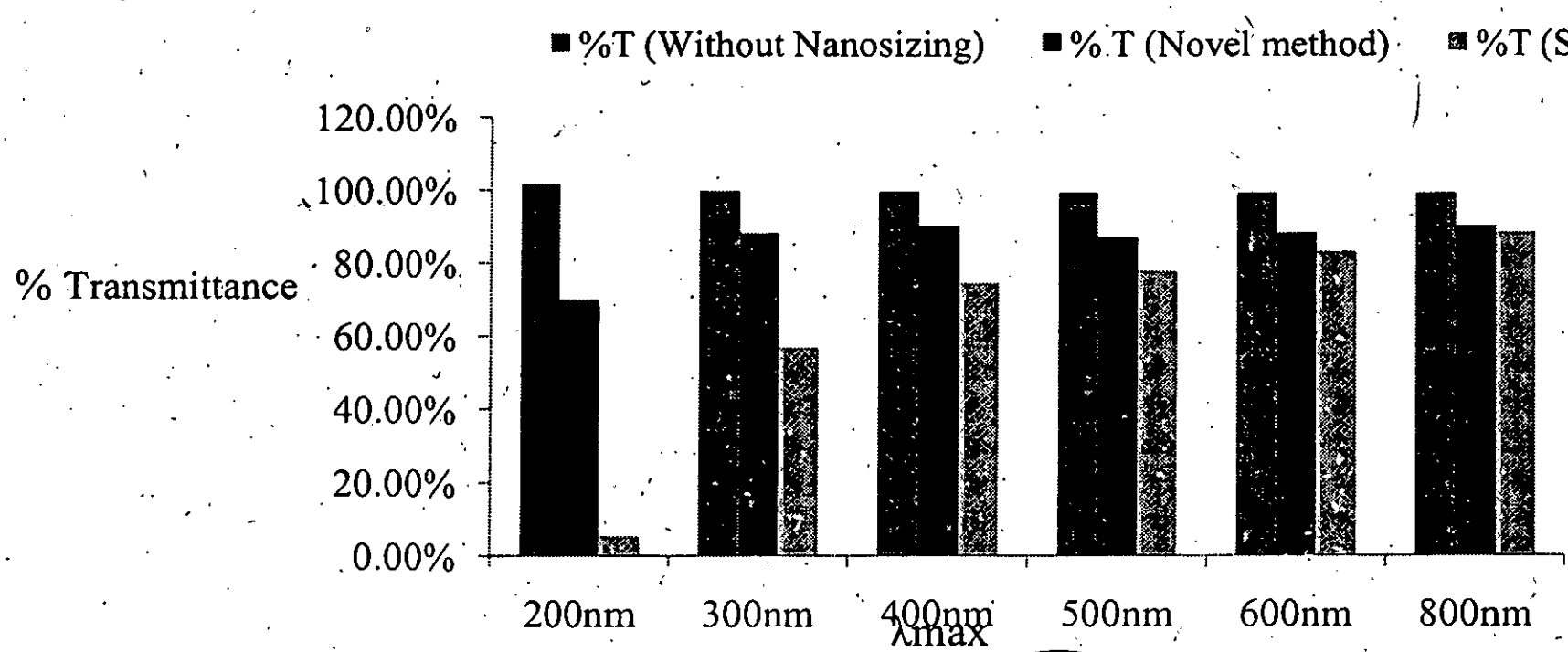
1. ZETA POTENTIAL OF TIAGABINE



Zeta Potential of Tiagabine: -9

Comparative Graph between %Transmittance and λ max of pure Tiagabine (without nanosizing) with nanosized Tiagabine (by novel sonication and standard solvent evaporation methods).

2. NANOSIZING OF TIAGABINE



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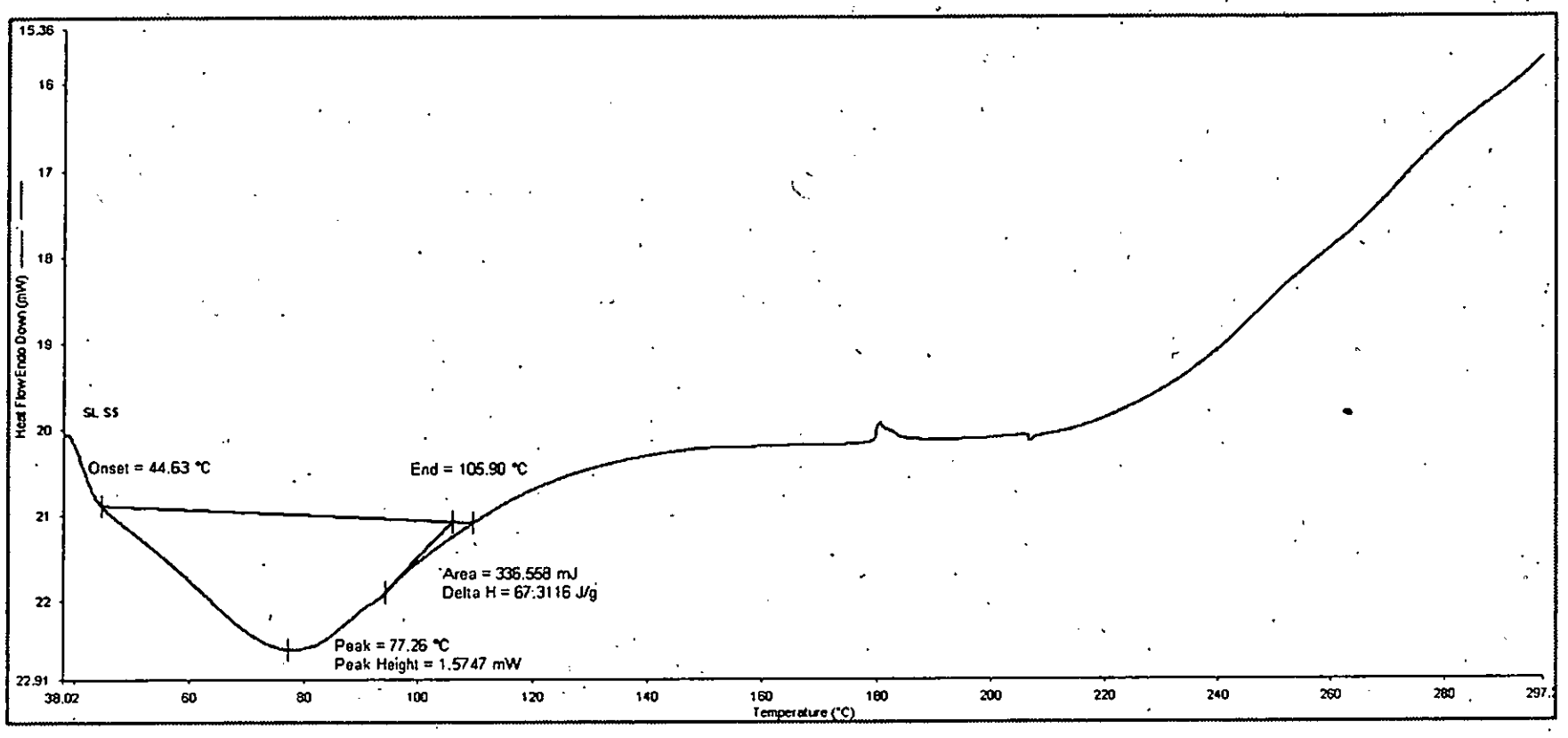
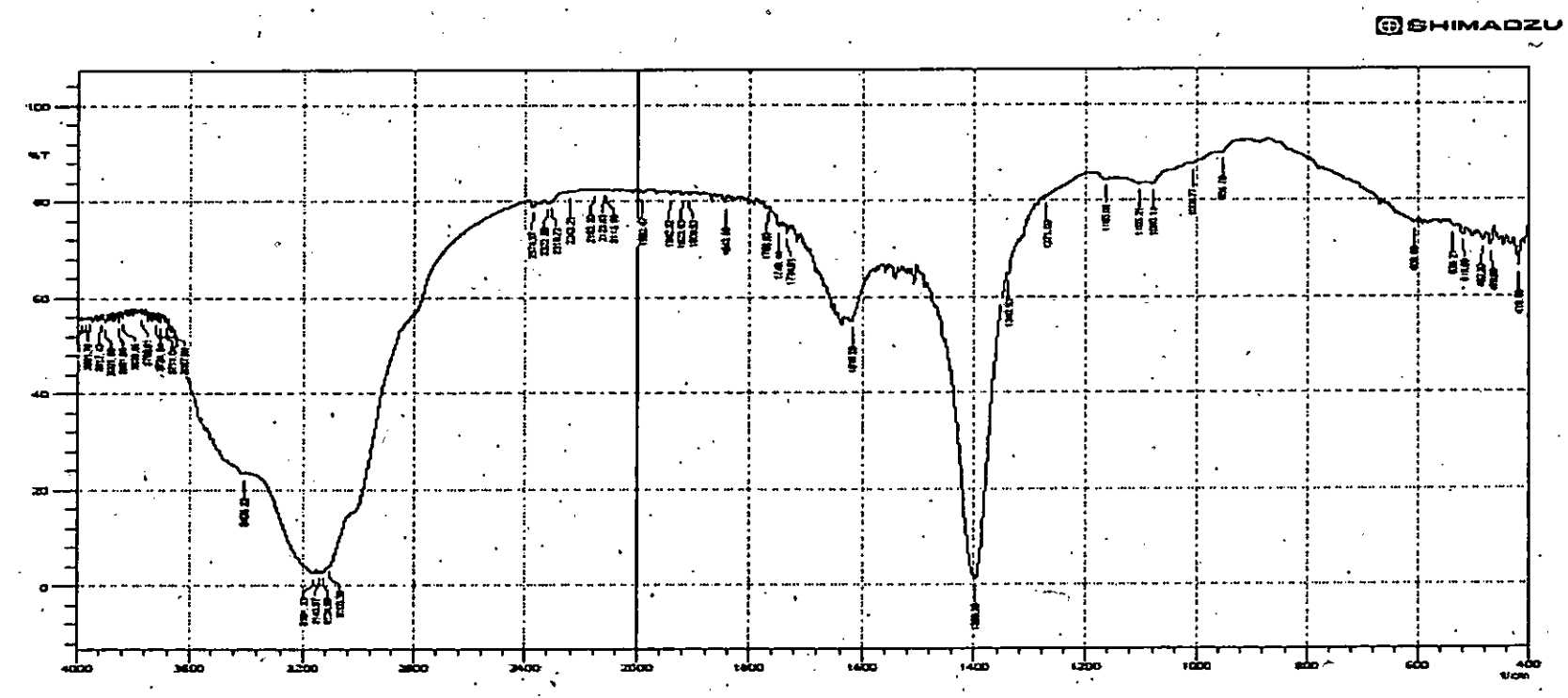
3. DIFFERENTIAL SCANNING CALORIMETRY OF SOLANUM LYCOPERSICUM BIOPOLYMER



4. IR SPECTROSCOPYOF SOLANUM LYCOPERSICUM BIOPOLYMER



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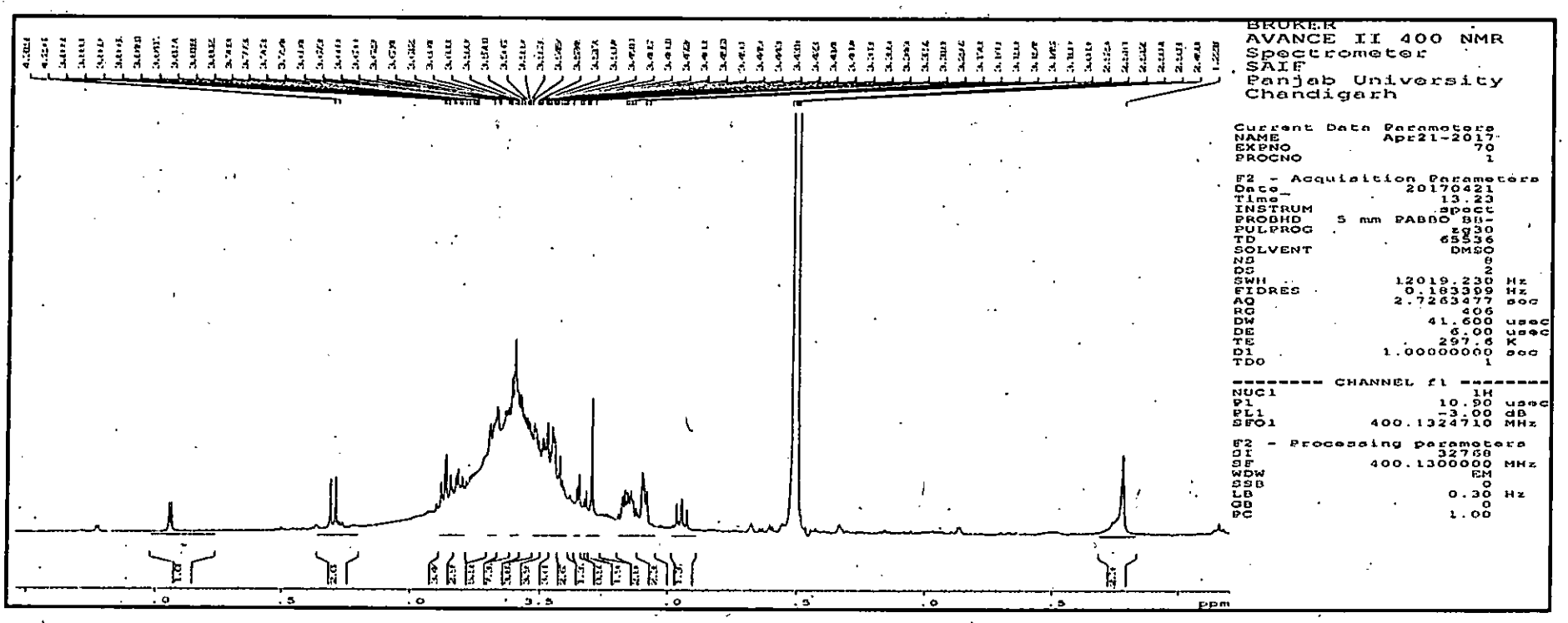
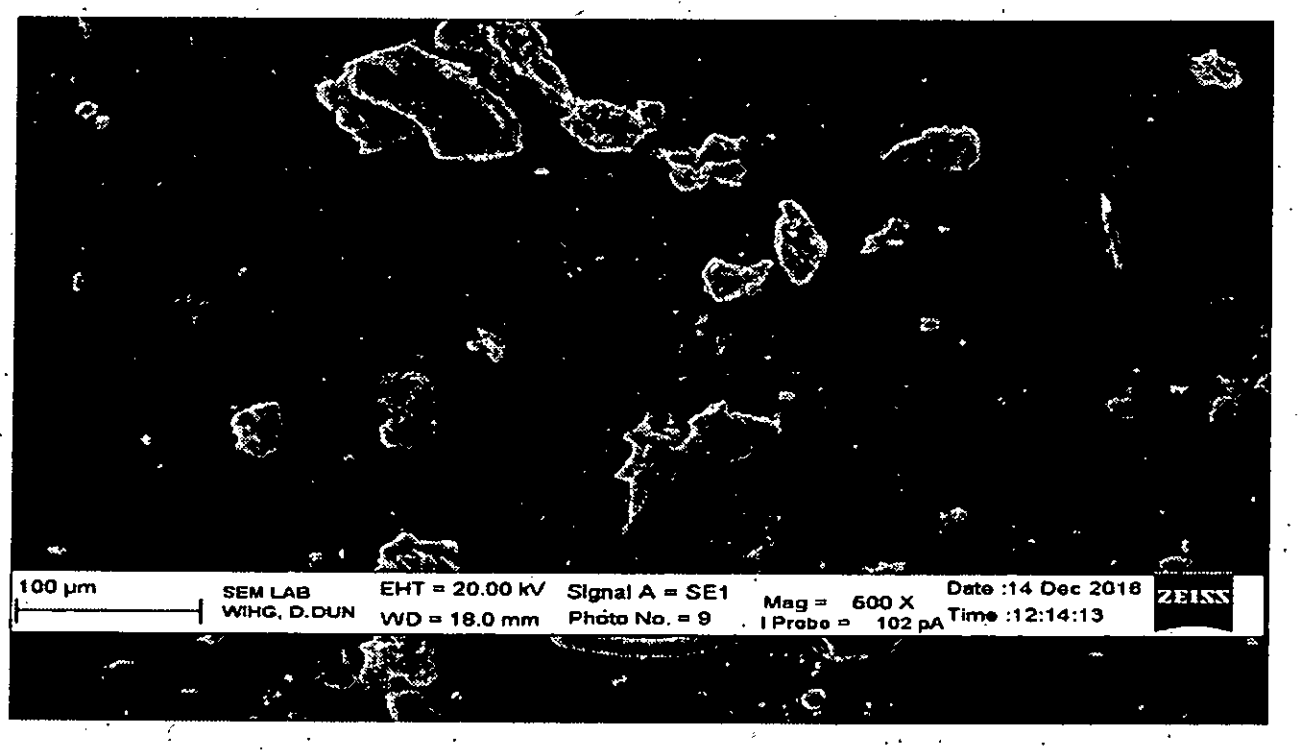
5. NUCLEAR MAGNETIC RESONANCE SPECTROSCOPYOF SOLANUM LYCOPERSICUM BIOPOLYMER



6. SCANNING ELECTRON MICROSCOPY OF SOLANUM LYCOPERSICUM BIOPOLYMER



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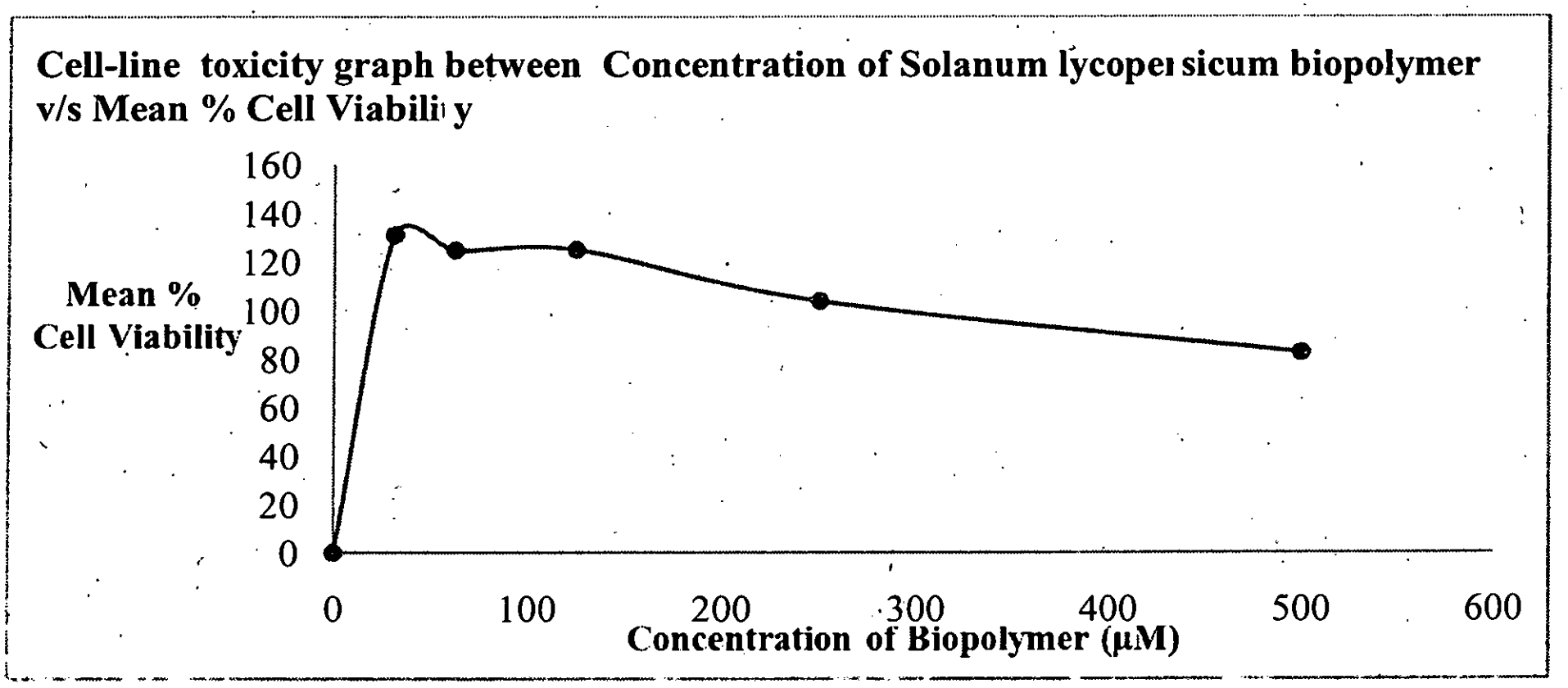
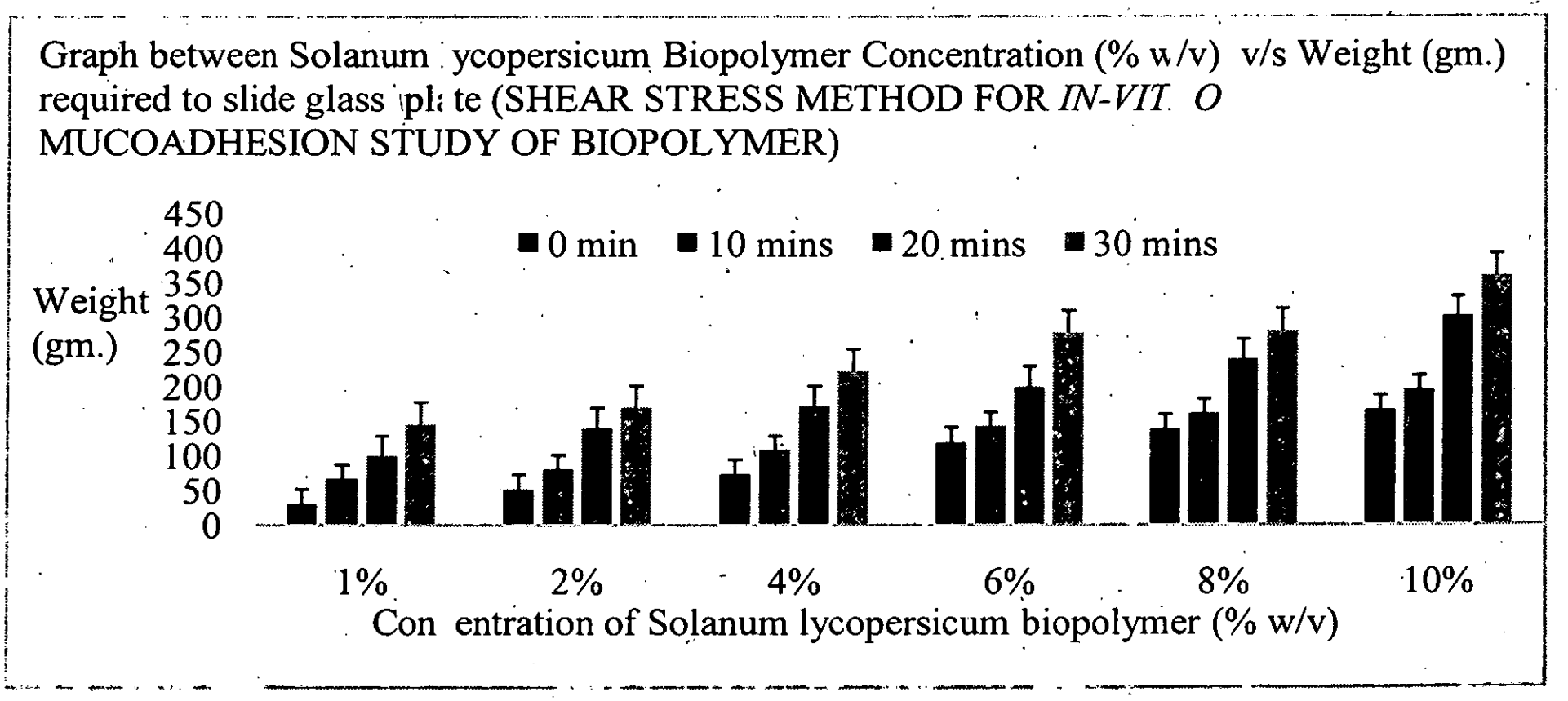
7. CELL-LINE TOXICITY OF SOLANUM LYCOPERSICUM BIOPOLYMER



8. MUCOADHESIVITY OF SOLANUM LYCOPERSICUM BIOPOLYMER



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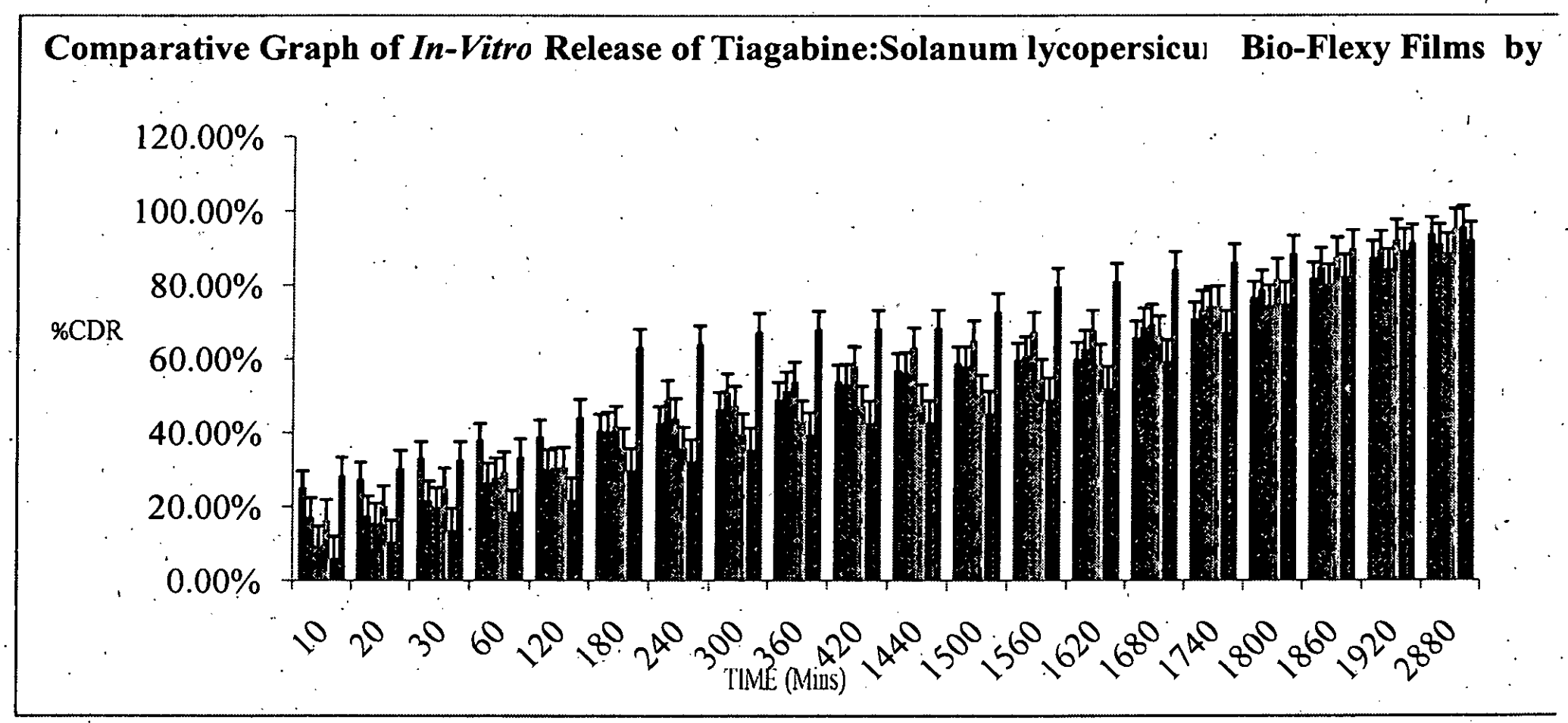
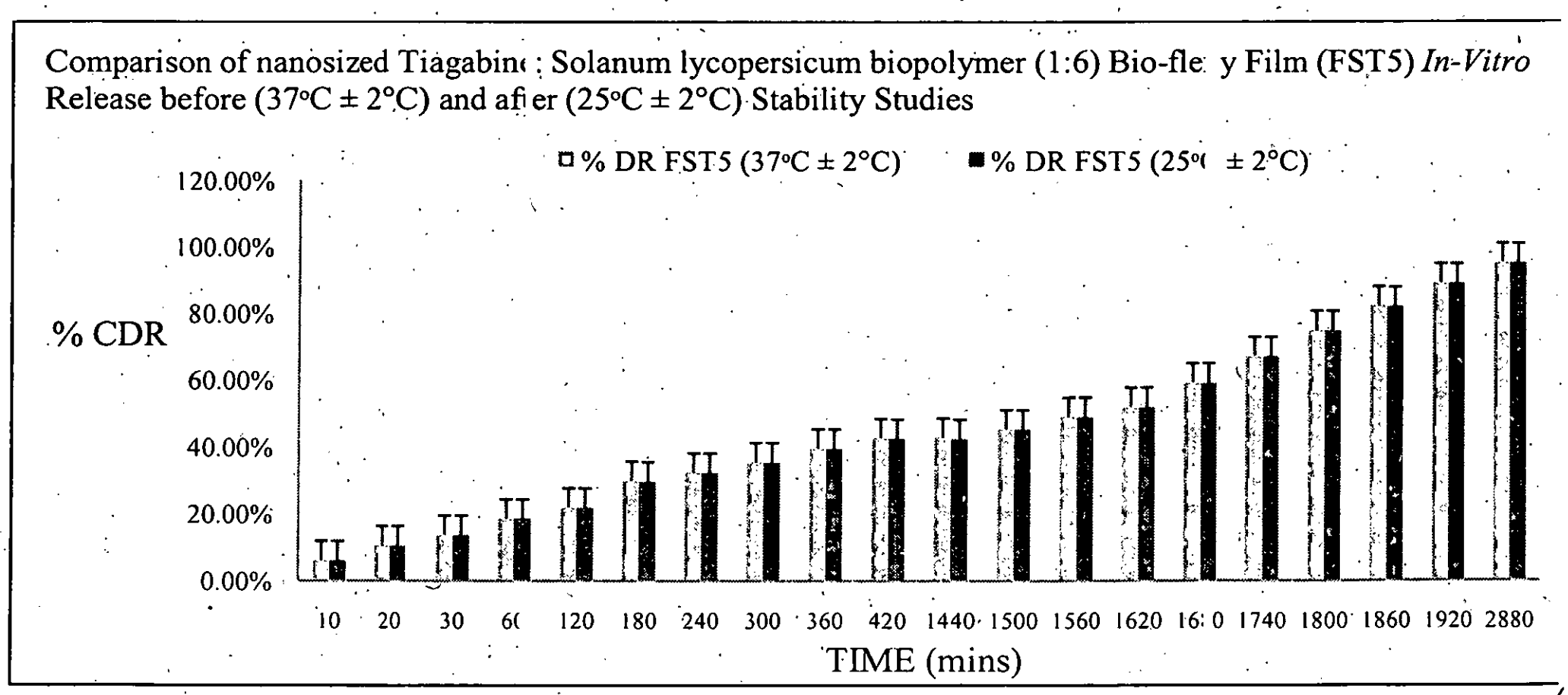
Dehradun (Uttaranchal)

9. KINETIC RELEASE OF TOPIRAMATE-SOLANUM LYCOPERSICUM BIOPOLYMERBIO-FLEXY FILMS



10.STABILITY STUDIES OF BEST FORMULATION OF NANOSIZED TIAGABINE LOADED BIO-FLEXY FILM CONTAINING SOLANUM LYCOPERSICUM BIOPOLYMER



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D.S.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

We claim: The invention claims:

1. A mucoadhesive system comprising of an antiepileptic moiety with one or more Co-processing agents derived from a natural edible source (Solanum lycopersicum i.e., tomato fruit pulp) as a bioretardant cum film former for Delivery of API to brain via Oro Trans- Soft Palatal platform.

2. The mucoadhesive system of Claim 1, where in it comprises of other co-processing agents dextrose, fructose as flexicizers, pectin as initiator at optimized concentration ranging from 1-3%.

3. The antiepileptic drug of the Claim 1, wherein chemically comprises of (*R*)-1-[4,4-bis(3-methylthiophen-2-yl)but-3-enyl] piperidine-3- carboxylic acid or Tiagabine at concentration of 1μg/cm^2 of the mucoadhesive device.

4. The bioretardant of Claim 1, which was isolated by a simplified economic process using optimized concentration of non-solvent dimethyl ketone in double proportion to aqueous extract and further bioretardant was recovered, characterized and showed in-built retardability, filmability and mucoadhesivity due to functional groups like RCOOH, RCONH2, C=C-COOH, S=O, RNH2, RCH2OH and GTT at 105.90°C.

5. The biomaterial spectral characterization of Claim 4 wherein comprises of mucoadhesive functional agents. The prolongability in Tiagabine release from the bio-flexy films was extended to 48 hours.

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

6. Tiagabine bio-flexy films of Claim 5 wherein show promising significant mucoadhesivity and mucoretentivity over a prolonged duration.

Director
Faculty of Pharmacy
Jamia Hamdard (Deemed)

Delivery of nanosized Tiagabine loaded Bio-flexy films using Bio-film former from Solanum lycopersicum bio-functional agent for Oro Soft Palatal Route.

ABSTRACT

The research work explores novel delivery approach for delivering Tiagabine via Trans-Soft Palatal route in form of Bio-flexy films for treatment of epilepsy. The formulations comprises of nanosized Tiagabine, Solanum lycopersicum mucoadhesive bio-film former, Flexicizers, Film Initiator and other co-processing agents and evaluated for various parameters. The prepared Formulations showed promising mucoadhesivity, filmability along with significant Pharmacokinetics and Pharmacodynamics Anticonvulsant activity on experimental animals.

Director
D.I.T.-Faculty of Pharmacy
Dehradun (Uttaranchal)

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Department of Industrial Policy & Promotion,
Ministry of Commerce & Industry,
Government of India

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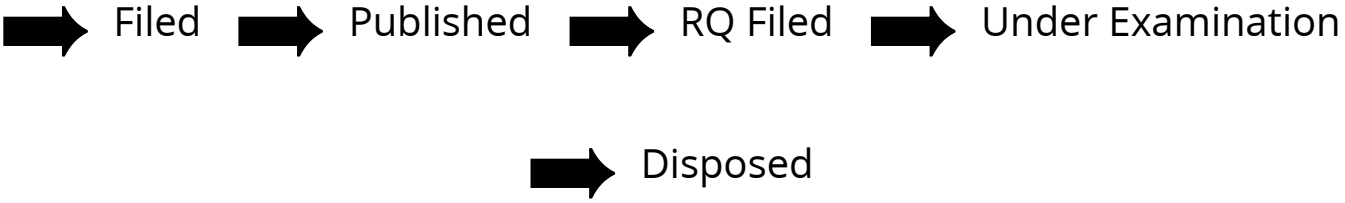
Application Details	
APPLICATION NUMBER	201911008672
APPLICATION TYPE	ORDINARY APPLICATION
DATE OF FILING	06/03/2019
APPLICANT NAME	1 . PROF.(DR.) N.V. SATEESH MADHAV 2 . DR. SUGANDHA VARSHNEY
TITLE OF INVENTION	DELIVERY OF NANOSIZED TIAGABINE LOADED BIO-FLEXY FILMS USING BIO-FILM FORMER FROM SOLANUM LYCOPERSICUM BIO-FUNCTIONAL AGENT FOR ORO SOFT PALATAL ROUTE
FIELD OF INVENTION	CHEMICAL
E-MAIL (As Per Record)	
ADDITIONAL-EMAIL (As Per Record)	dit@dituniversity.edu.in
E-MAIL (UPDATED Online)	
PRIORITY DATE	
REQUEST FOR EXAMINATION DATE	--
PUBLICATION DATE (U/S 11A)	11/09/2020

Application Status	
APPLICATION STATUS	Awaiting Request for Examination

			View Documents



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