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SMART APPROACH FOR PREPARING NANOSIZED LOADED TIAGABINE USING A BIO-FLEXY FILM FORMER FROM GREEN BRINJAL POLYMER AND ITS *IN-VITRO* PERFORMANCE

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ABSTRACT
The research work aimed to formulate bio-flexy films loaded with nanosized tiagabine using a novel biopolymer isolated from Solanum melongena pulp. Tiagabine**,** anticonvulsant drug possesses $t_{1/2}$:7-9 hours (low); protein binding: 96%; water solubility: 22mg/L, acts as selective GABA reuptake inhibitor. Side effects include abdominal pain, pharyngitis, suicidal thoughts and sudden unexpected death. Biopolymer isolated from Solanum melongena was used to prepare bio-flexy films because of its biodegradability, biocompatibility, non-toxic, non-irritant nature and non-reactive on soft palatal surface. Physicochemical characterization of biopolymer displayed inbuilt properties of filmability, mucoadhesivity. Bio-flexy films were prepared by solvent casting technique. Drug to polymer ratio was chosen at five levels for Solanum melongena **FSM1-FSM5** containing varying ratios of biopolymer from 1%-10% and 1% of nanosized tiagabine and compared with Sodium CMC standard films. Bio-flexy films were evaluated for thickness, surface pH, weight uniformity, folding endurance, *in-vitro* release and stability studies. The percentage yield of Solanum melongena biopolymer was found to be 2.24±0.01%. Thickness of formulated bio-flexy films was ranging from 0.019 mm to 0.076 mm, folding endurance: 86-114, surface pH: 7.01±0.02 to 7.01±0.01, weight uniformity: 0.001±0.02 to 0.032±0.01. Based on all above mentioned evaluation parameters, **FSM3** (containing Tiagabine: Solanum melongena biopolymer (1:5)) having $\mathbf{R^2}$**=0.9770**, peppas korsmeyer as best fit model, follows Fickian diffusion (Higuchi matrix) release mechanism using BITS Software 1.12.Stability study revealed stable bio-flexy films with no significant change in physical appearance and stable pH. Prepared formulations of tiagabine loaded bio-flexy films are suitable for soft palatal delivery.

KEYWORDS: Bio-flexy films, nanosized tiagabine, Solanum melongena biopolymer, soft palatal delivery.

1. INTRODUCTION
Direct brain targeting of drug via intra and inter-neural pathway, crossing BBB, decreases drug's side effects and increases its therapeutic effect.

Although various routes of mucoadhesive drug delivery such as ocular, nasal, vaginal, rectal offer certain advantages, but the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. On the other hand, the oral cavity is very attractive, feasible site for systemic drug delivery, highly acceptable by patients. The oral mucosa is relatively permeable, robust, shows short recovery times after stress or damage, the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. Oral trans-mucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract.

The oral mucosa is categorized into sublingual, gingivae, buccal and soft palate mucosa. The buccal and sublingual dosage form short acting because of the limited contact between the dosage form but provide rapid onset of action and improve the efficacy and drug safety. These routes are considered unsuitable for prolonged administration whereas soft palate drug delivery at steady state infusion of drug over an extended period of time because the soft palate to cover a epiglottis while swallowing, it is more fitted for sustained and controlled drug delivery system.[1] The soft palate has non-keratinized histology, no bone, enriched blood and neural supply, drug directly reaches systemic circulation, non-invasive, non-mobile with highly mucoretention ability, afford high bioavailability, lower doses, offers a Novel Drug Delivery Platform for Brain targeting. Therapeutic potential of many drugs can be improved by this route. It is a promising area for systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide

and protein drug molecules.[2] When nanosized drug is administered by this route, then, it can directly reach into brain by via inter and intra neural pathway. Trigeminal nerve directly connects soft palate to brain.[3]

At present **Epilepsy** is cause of 3.3% total deaths worldwide, ranking 7th position that is expected to rise at 6th position causing 3.7% of total deaths till year 2030. Tiagabine, an anticonvulsant drug available as tablets and capsules dosage forms only which shows delayed action due to First Pass Metabolism in GIT.

In this research work, an inert, biodegradable cost effective biopolymer obtained from SOLANUM MELONGA pulp was used. SOLANUM MELONGA contains vitamins, minerals, dietary fibre, proteins, antioxidants, glucoside, phenolic compounds (caffeic, chlorogenic), flavonoids (nasunin, delphindin), carbohydrates, vitamin A, linoleic, omega 3 and omega 6 fatty acids, folate, calcium, magnesium, phosphorus, potassium, glutamate and proline.[4]

Nanosized tiagabine loaded Bio-flexy films were suitably formulated that can provide sustained drug action up to 2 days. It can decrease dose frequency and can also minimize adverse drug reactions..[5]

Importance and Advantages of using Biopolymer instead of using Synthetic Polymers like CMC and HPMC[6]

1. Solanum melongena biopolymer is having uniqueness of being pure, natural origin isolated from green brinjal pulp.
2. Isolated biopolymer exhibited significant inbuilt mucoadhesivity, filmability, retardability and biodegradability comparable to synthetic polymers.
3. Economically cheap and environment friendly.
4. Suitable as a drug carrier for formulation of bio-flexy films, provides sustained release.
5. It can be commercialized effectively in Pharmaceutical Industries.
6. Solanum melongena biopolymer isolated using acetone as solvent that belongs to Class 3 so is less toxic, possess lower risk to human health. No class 1, 2 carcinogenic solvents used.
7. HPMC, CMC are synthesized using various harmful chemicals. Thus, toxicity that is by synthetic polymers can be avoided by using biopolymer.

Similar study about using this biopolymer for preparation of Mucoadhesive Drug Delivery Systems

No similar study is available for this biopolymer as we are pioneer to isolate biopolymer from Green brinjal pulp.

2. MATERIALS AND METHODS

DRUG: Tiagabine (procured from Sun Pharmaceuticals Industries Ltd., Gujarat).

POLYMERS

SOLANUM MELONGA biopolymer (Green brinjal procured from local market).

Sodium Carboxyl Methyl Cellulose (Central drug House (P) Ltd. New Delhi).

All other reagents used were of highest purity and analytical grade. Double distilled water was used throughout the experimental work.

2.1 Isolation of biomaterial from SOLANUM MELONGA

- Weighed 250gm of Solanum melongena, removed skin. Prepared slurry using 500mL of distilled water filtered using muslin cloth.
- Added optimized quantity of propan-2-one in ratio of 1:2 to filterate. Refrigeration for 24hrs. Centrifugation at 3500rpm for 15 mins. Discarded supernatant and collected the residue.
- Kept biomaterial for natural drying for 24 hrs, powdered, passed through Sieve No. 120, packed and stored. Optimized six times, reported % yield.

This method is cost effective if raw material is abundantly collected during the season and cost will be viable when compared to synthetic/semi-synthetic polymers

2.2 Physicochemical Characterization

The Physiochemical characterization of isolated bio-material was performed like colour, odour, solubility, melting point and various chemical tests were performed.[6]

i) Test for carbohydrates

Molisch Reagent Test

2mL of biopolymer solution (0.1gm dissolved in 2mL of distilled water) was taken in a test tube. 2 drops of Molisch reagent (Solution of ∝-napthol in 95% ethanol) was added. Solution was then poured slowly into a test tube containing 2mL of concentrated sulfuric acid. Two layers were formed. Purple colour appeared at interface of the two layers due to formation of 5-hydroxy methyl furfural.

ii) Test for proteins

Biuret Test

This test determines the presence of **peptide bonds** in protein content in the isolated biomaterial. 2mL of biomaterial solution (0.1gm dissolved in 2mL of distilled water) was taken in a test tube. 1 mL of sodium hydroxide solution (1%) followed by 1% copper (II) sulphate solution was added drop wise. Test tube was then shaken vigorously.

Allowed the mixture to stand for 5 minutes and observed the colour change. Biuret test is based on the ability of Cu (II) ions to form a violet-coloured **chelate complex** with peptide bonds (CONH groups) in alkaline

conditions. The chelate complex absorb light at **540 nm** so it appeared **violet**. Colour change from blue to violet indicated presence of that proteins.

iii) Test for starch

2 mL of biomaterial solution (0.1gm dissolved in 2mL of distilled water) was taken in a test tube.1-2 drops of iodine solution was added. Then observed the colour change. Appearance of an intense blue black colour confirmed the presence of starch in isolated biomaterial (transfer of charge between starch and iodide ion changes the spacing between the energy orbitals, so starch-iodide complex absorb light at higher wavelength).

iv) Test for reducing sugar

2mL of biopolymer solution (0.1gm dissolved in 2mL of distilled water) was taken in a test tube. 1mL each of Fehling's A (7g $CuSO_4.5H_2O$ dissolved in distilled water containing 2 drops of dilute sulfuric acid) and Fehling's B (35gm potassium tartrate, 12gm of sodium hydroxide in 100 mL of distilled water) were added. The test tube was placed in a water-bath at 60°C. Appearance of brick red precipitate of insoluble copper oxide indicated the presence of reducing sugar in isolated biomaterial.

Drug-Excipient Interaction Study[5]

Drug-excipient interaction study was performed by taking three different ratios of drug and bio-material 1:1, 1:3 and 3:1.The U.V. absorbance of the three ratios was taken and compared with the absorbance of pure drug.

a) Wet method

Drug-excipient in the ratio of 1:1, 1:3 and 3:1 were taken in 3 different petridishes. 1mL of distilled water was added to wet the mixtures. Mixtures were then subjected to drying in oven for 30mins at 50°C, followed by dilution with 2mL of methanol. Ultraviolet Spectroscopy study was performed. The shift in λ_{max} was reported in comparison to that of pure tiagabine.

b) Dry method

Drug-excipient in the ratio of 1:1, 1:3 and 3:1 were taken in their physical forms (dry) in 3 different petridishes. Mixtures were kept at room temperature for 2hrs. followed by dilution with 2mL of methanol. Ultraviolet Spectroscopy study was then performed. The shift in λ_{max} was reported in comparison to that of pure Tiagabine.

Importance of determination of drug-biopolymer interaction by Dry and Wet methods

The two methods revealed that no interaction of drug-biopolymer occurred either in dry form on in presence of solvent. Since biopolymer is isolated from natural source and used in formulation, it has to be ascertained whether the biopolymer is inert in both dry (during storage) as well as wet (if used in oral drug delivery) conditions. Thus to confirm inertness and non-reactiveness of biopolymer with drug, these two methods had been performed. The drug was found to be intact with biopolymer.

2.4 Spectral studies of isolated biopolymer[6,7]

IR SPECTROSCOPY

In this technique a small amount of biopolymer was intimately mixed with 100 times of its weight of powdered potassium bromide, prepared 1-2mm thick and 1cm diameter pellet. The spectra was scanned in the wave no range 3500-400 cm^{-1}.

SEM Analysis

Morphological examination of the surface and internal structure of the biomaterial was performed by using a scanning electron microscope (SEM). A small amount of biomaterial was fixed on aluminum studs and it was coated with gold using a sputter coater under vacuum (pressure: 1mm Hg). The biomaterial was then analyzed by SEM.

NMR Spectral Analysis

Nuclear magnetic resonance is a physical phenomenon in which magnetic nuclei in a magnetic field absorb and re-emit electromagnetic radiation. This energy is at a specific resonance frequency which depends on the strength of the magnetic field and the magnetic properties of the isotope of the atoms; in practical applications, the frequency is similar to VHF and UHF television broadcasts (60–1000 MHz).

Figure 1: NMR Spectrometer

Differential scanning calorimetry (DSC) is a thermo analytical technique in which the difference in the amount of the heat required to increase the temperature of a sample and reference is measured as a function of temperature. It was performed for determination of Glass Transition temperature (GTT or Tg). For DSC the Perkin Elmer Instrument, Model-JADE DSC will be used, with the Heat flow of 50-250°C at the rate of 10°C/minute and Nitrogen flow rate of 20ml/minute will be used.

2.5 Conversion of Tiagabine Hydrochloride into Tiagabine by Precipitation Method

To 100mg of tiagabine hydrochloride, 20mL of distilled water was added in a test tube and shaken vigorously. Mixture was subjected to sonication for 1 cycle (each

cycle of 3mins) in ultrasonic bath sonicator. 10mL of 1N sodium hydroxide solution was incorporated drop wise in above Tiagabine solution. Precipitate was formed at bottom of test tube. Mixture was centrifuged for 15mins. at 3500rpm. Tiagabine was separated, washed with 10ml distilled water and air dried.

2.6 Preparation of Standard Curve of Tiagabine[7,8]

10mg of tiagabine was dissolved in 30mL of distilled water in a 100mL volumetric flask and diluted up to the mark with distilled water (100µg/mL).Dilutions of Concentrations (0.5,1,2,3,4 and 5µg/mL) were prepared in 10mL volumetric flasks. Volume was made up to 10mL with distilled water (λmax =257nm). Absorbance was measured against solvent blank.

Distilled Water was used as solvent for standard graph preparation because drug showed maximum solubility in distilled water.

Nanosizing of tiagabine by novel method

100mg tiagabine was mixed with 10mg dextrose, 5mg fructose and 10mL distilled water in mortar pestle and triturated. The mixture was transferred into beaker, sonicated for 5 cycles (3mins/cycle in ultrasonic bath sonicator). Mixture was diluted with 50mL distilled water and again sonicated for 5 cycles. Absorbance, % Transmittance, % Blockage (100- %Transmittance) was noted after every 5 cycles up to 15 cycles. After 15th cycle, residue was collected, dried, packed and stored.

Nanosizing of tiagabine by standard method

100 mg Tiagabine was mixed with 10mg dextrose, 5mg fructose and 10mL methanol in mortar pestle and triturated. The mixture was transferred into beaker, sonicated for 5 cycles (3mins/cycle in ultrasonic bath sonicator). Mixture was diluted with 50mL distilled water and again sonicated for 5 cycles. Absorbance, % Transmittance, % Blockage (100- %Transmittance) was noted after every 5 cycles up to 15 cycles. After 15th cycle, residue was collected, dried, packed and stored.

The main purpose of Nanosizing tiagabine by two different methods was to compare novel method with published standard solvent evaporation method.

2.6 FORMULATION OF BIO-FLEXY FILMS (solvent casting method)

Nanosized tiagabine (0.1gm/100ml) and SOLANUM MELONGA biopolymer solution (10%w/v) (in ratios 1:1, 1:3, 1:5, 1:6, 1:10) were taken in mortar. To this mixture, dextrose (film initiator) (10mg/mL), fructose (5mg/mL) were added and triturated. Added glycerine (10µl) (plasticizer), pectin (3%) (Film former). Distilled water (20mL) was incorporated, uniformly triturated for 2mins. Mixtures were subjected to magnetic stirring for 15mins, followed by sonication for up to 5 cycles (each cycle 3minutes). Mixtures were poured into petridishes and kept for drying. Prepared films were removed from petridishes by using 1% borax solution. Checked the filmability of prepared films.

TABLE: 1 Formulation of Bio-flexy films using (SOLANUM MELONGA) biopolymer

Formulation	FSM1 (1:1)	FSM2 (1:3)	FSM3 (1:5)	FSM4 (1:6)	FSM5 (1:10)
Tiagabine (mg)	100	100	100	100	100
SOLANUM MELONGA biopolymer (mg)	100	300	500	600	1000
Dextrose (mg)	100	100	100	100	100
Fructose (mg)	50	50	50	50	50
Glycerine (µl)	10	10	10	10	10
Distilled Water (mL)	10	10	10	10	10

TABLE 2: Formulation of Bio-flexy film using Sodium CMC as a synthetic polymer

Formulation	FS1 (1:1)	FS2 (1:3)	FS3 (1:5)	FS4 (1:6)	FS5 (1:10)
Tiagabine (mg)	100	100	100	100	100
Sodium CMC (mg)	100	300	500	600	1000
Dextrose (mg)	100	100	100	100	100
Fructose (mg)	50	50	50	50	50
Glycerine (µl)	10	10	10	10	10
Distilled Water (mL)	10	10	10	10	10

Same procedure as SOLANUM MELONGA was followed for formulation

2.7 EVALUATION OF FORMULATED BIO-FLEXY FILMS[9]

2.7.1 Thickness

The thickness of randomly selected bio-flexy film from every batch was determined using standard digital micrometer. The average thickness was determined and reported with appropriate standard deviation.

2.7.2 Folding endurance

Folding endurance of bio-flexy films was determined by repeatedly folding one of the film at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good properties. The number of times of film could be folded at the same place without breaking gave the value of the folding

endurance. This test was done on randomly selected three flexi film from each batch.

2.7.3 Surface pH study

The surface pH of Bio-flexy films was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may causes irritation to the soft palatal mucosa, it was determined to keep the surface pH as close to neutral as possible. The bio-flexy films were allowed to swell by keeping it in contact with 1ml of distilled water for 1hour at room temperature. The pH was measured by bringing the electrode in contact with the surface of film and allowing it to equilibrate for 1minute. The experiments were performed in triplicate and avg. values were reported.

Surface pH of films was determined because prepared bio-flexy films will be directly placed in soft palatal region, thus it is essential for formulation (rather than polymeric solution) to be neutral to mucosal surface and compatible with soft palatal pH.

2.7.4 Weight uniformity study

Weight uniformity of bio-flexy films determined by taking weight of ten bio-flexy films of sizes 1 square cm diameter from every batch and weight individually on electronic balance. The avg. weight was calculated.

2.7.5 *In-Vitro* Drug Release (by Modified M .S. Apparatus)[10,11]

A thermostatically controlled compartment with vials containing buffer pH 7.4 was prepared. Egg membranes tied to donor compartment (contained formulations) inserted into receiver compartment. Temperature was maintained at 37ºC using orbital shaker incubator. Samples were withdrawn at regular intervals ranging from 10mins to 30hrs.Complete Replacement of buffer each time. U.V. Spectral analysis was performed.

2.7.6 Stability Studies

Stability studies were conducted as per ICH Guidelines. Stability testing of pharmaceutical product is done to ensure the efficacy, safety and quality of active drug substance and dosage forms and shelf life or expiration period. The stability studies of the formulations were conducted at 40^{o}C ± 2^{o}C and ± 45± 5% RH, 25± 2^{o}C and 60 ± 5% RH and 2 ± 5^{o}C temperature and RH values respectively. After every15 days, the aggregation, nature, colour change, and in-vitro drug release of formulations was determined.[12,13]

3. RESULTS AND DISCUSSION

3.1 Isolation of Biomaterial

The % yield for biomaterial from SOLANUM MELONGA was found to be **2.24±0.01%.**

3.2 Physicochemical Properties of Isolated Biomaterial

The biomaterial obtained from pulp of SOLANUM MELONGA was obtained in powdered texture, dark brown in colour, odourless and soluble in acetone. Colour Changing Point was found to be 160±4ºC.

3.3 Drug Excipient Interaction Studies

Drug-polymer interaction study of biomaterial isolated was done by UV techniques. Drug interaction study was performed by using wet and dry method.

a) Wet method: λ_{max} was observed at 260nm, no significant difference than that of pure drug.
b) Dry method: λ_{max} was observed at 260nm, no significant difference than that of pure drug.

Thus, no drug-excipient interaction occurred.

3.4 Colorimetry

To 0.05gm of tiagabine, 0.05ml each of potassium permanganate, crystal violet, iodine, copper sulphate, potassium dichromate, methyl red, methyl orange, ferrous sulphate were incorporated on different sections of glass plate. Drug showed colour change with potassium permanganate from pink colour to brown colour depicting reaction of potassium permanganate due to saturation of double bonds. Drug (0.05gm) + Polymer (0.05gm) also showed similar colour change with potassium permanganate. This revealed that drug is not entrapped. After performing the UV method shows λmax of drug-excipient mixture near about pure drug. So drug-excipient interaction study showed that there was no interaction between drug and biomaterial and biomaterial was compatible with the drug. As no any interaction was found, so it indicated that the bio-material was found useful in formulation bio-flexy films. Drug + Polymer showed no colour change with other reagents.

TABLE: 3 Drug Polymer interaction with different reagents.

Potassium Permanganate	Crystal Violet	Iodine	Copper Sulphate	Potassium Dichromate	Methyl Red	Methyl Orange	Ferrous Sulphate
Pink to brown colour change	Purple	Light brown	Blue	Light colour change	Red	Brown	Light brown

Spectral studies of the isolated Bio-materials

IR Spectroscopy (using IRPal2.0 Software) The result of IR spectra of biomaterial isolated from Solanum melonga showed the peak at 1685 cm^{-1}, 1045 cm^{-1}, 1095 cm^{-1}, 1539 cm^{-1}, 1434 cm^{-1} 819 cm^{-1}, 1041 cm^{-1}, 1036 cm^{-1} with functional groups RCONH2, RCH2OH, R2CHOH, NO, S=O, R-Cl, RNH_2, RCOOH. The presence of these groups in isolated biomaterial indicated inbuilt mucoadhesive property.

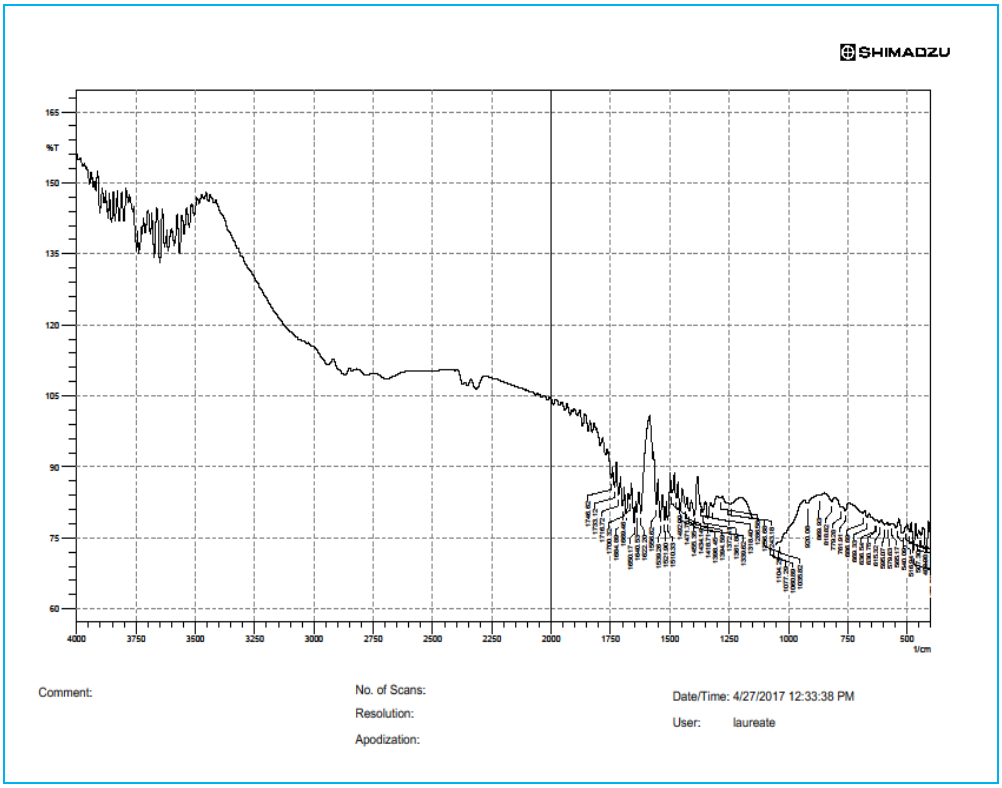

Figure 2: IR Spectra of SOLANUM MELONGA biopolymer

NMR

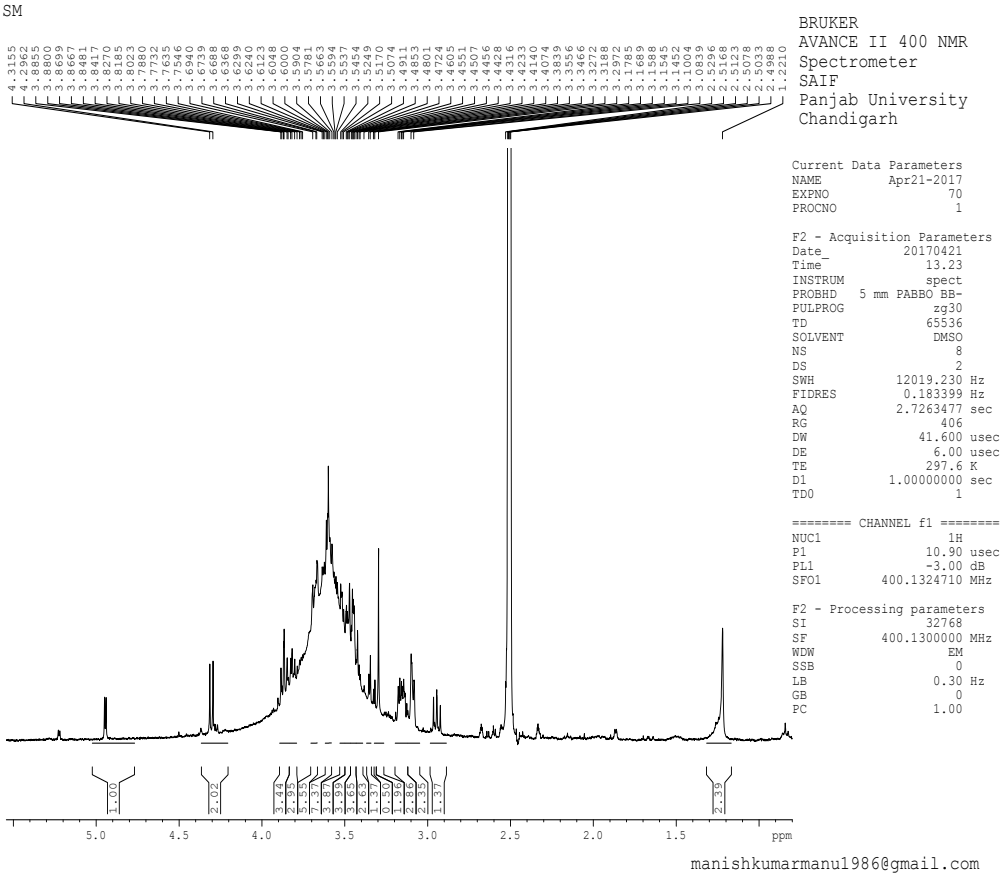

Figure 3: NMR Spectral data of Solanum melongena biopolymer

DSC

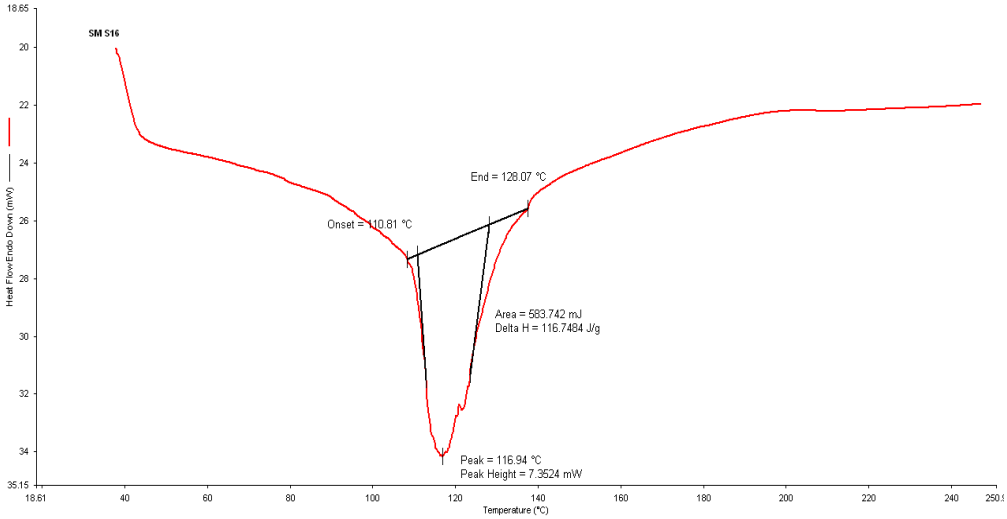

Figure 4: DSC of Solanum melongena Biopolymer

Peak was found to be at 116.94ºC.

Preparation of Calibration Curve of Drug

Calibration curve of Tiagabine was prepared in distilled water showed linearity. R^2 value was found to be **0.9311.**

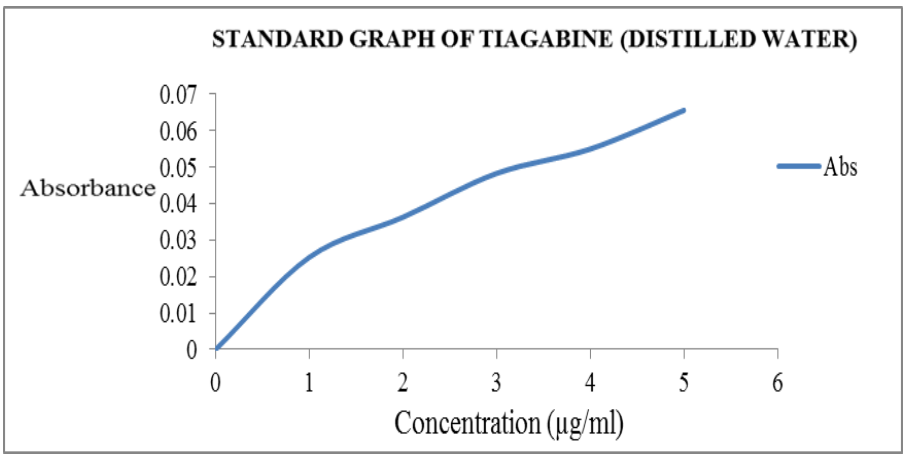

Figure 5: Standard curve of Tiagabine in Distilled Water

Nanosizing of Tiagabine

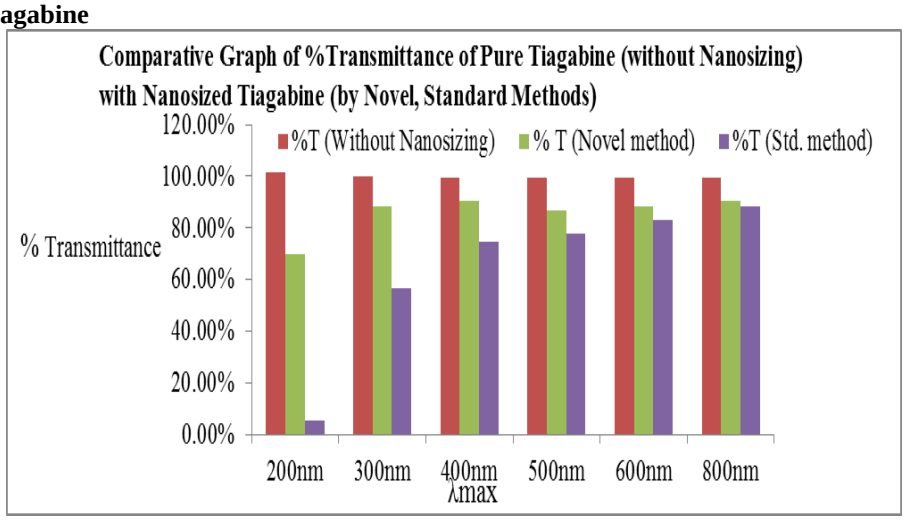

Figure 6: Comparative Graph between %Transmittance and λ max of pure tiagabine (without nanosizing) with nanosized Tiagabine (by novel and standard methods)

Zeta Potential:

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -11.9	Peak 1:	-11.9	100.0	4.82
Zeta Deviation (mV): 4.82	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 2.76	Peak 3:	0.00	0.0	0.00

Result quality : Good

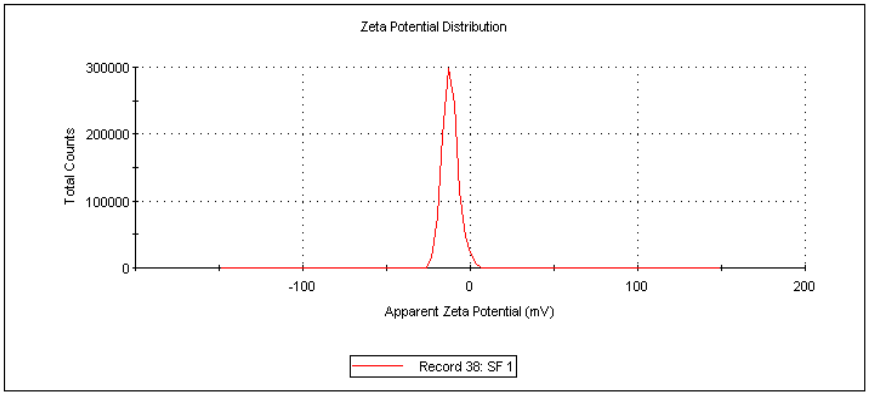

Figure 7: Zeta potential of nanosized drug

z-sizing was performed and zeta potential was found to be –11.9mV

Thickness of formulations

Thickness of nanosized tiagabine loaded bio-flexy films containing SOLANUM MELONGA biopolymer **(FSM1-FSM5)** was in range of 0.019 mm to 0.076 mm. Thickness of **Sodium CMC** containing bio-flexy Films **(FS1-FS5)** was found to be in range of 0.020-0.038 mm.

Folding endurance of formulations

The folding endurance was obtained in the range of 86-114for nanosized tiagabine loaded Bio-flexy films containing SOLANUM MELONGA biopolymer **(FSM1-FSM5)**. The folding endurance was obtained in the range of 122-135 for formulations containing **Sodium CMC (FS1-FS5)** biopolymer.

Surface pH of formulations

Surface pH of nanosized tiagabine loaded bio-flexy films containing SOLANUM MELONGA biopolymer **(FRP1-FRP5)** was found to be in range of 7.01±0.02 to 7.01±0.01.The pH was obtained in the range of 7.2±0.20 to 7.5±0.05 for bio-flexy films using **Sodium CMC (FS1-FS5)** synthetic polymer. Prepared formulations suitable for soft palatal delivery platform as they are in the range of physiological pH.

Weight Uniformity of formulations

Weight of nanosized tiagabine loaded bio-flexy films containing SOLANUM MELONGA biopolymer **(FSM1-FSM5)** was found to be in range of 0.001±0.02 to 0.032±0.01 and that of **Sodium CMC (FS1-FS5)** was found to be in range of 0.011±0.03 to 0.032±0.05.

***In-Vitro* Release Study by Modified M.S. Apparatus**

Best Formulation was found to be **FRP3** (Bio-Flexy film containing **Tiagabine: SOLANUM MELONGA** biopolymer in ratio of 1:5).

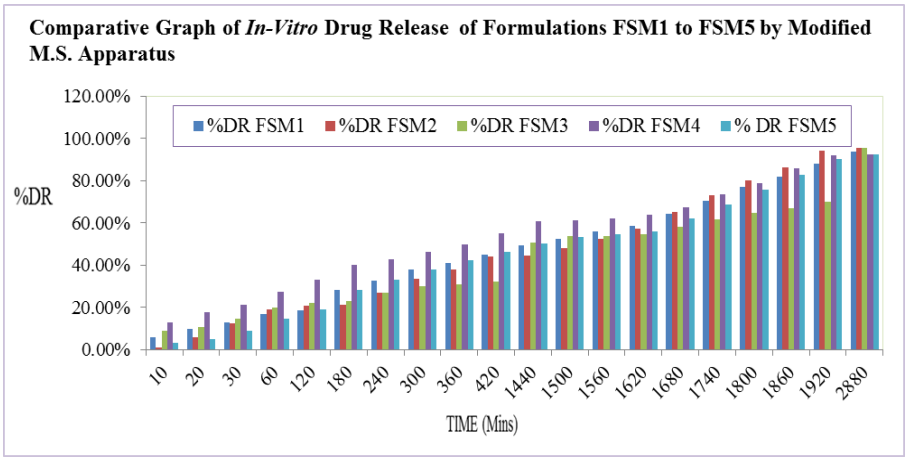

Figure 8: *In-Vitro* drug release of tiagabine bio-flexy films using SOLANUM MELONGA biopolymer by Modified M.S. Apparatus (dynamic method) (FSM1-FSM5)

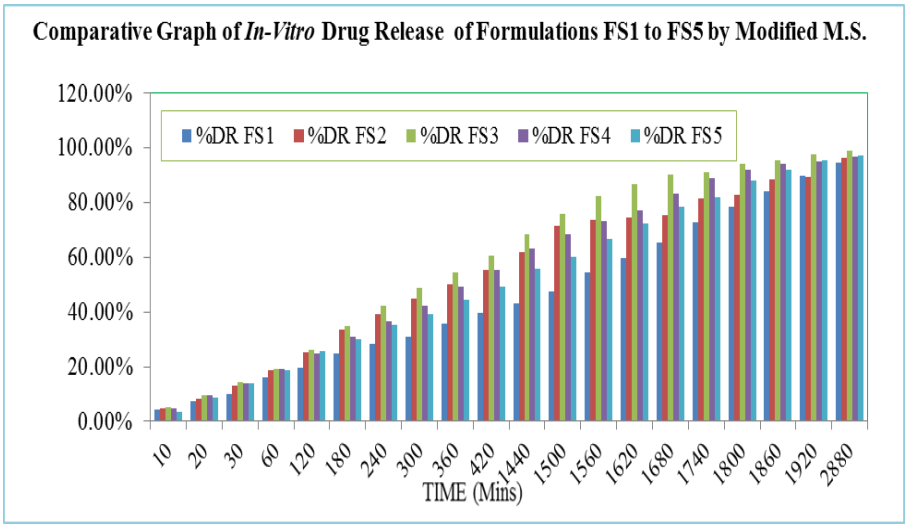

Figure 9: *In-Vitro* drug release of tiagabine bio-flexy films using Sodium CMC by Modified M.S. apparatus (dynamic method) (FS1-FS5)

Stability studies

The formulations examined showed no physical changes, related to the colour, odour, taste etc. The drug content and *in-vitro* release was found to be the same, no significant change was observed. So it was concluded that the formulation bio-flexy films of tiagabine was found to be stable.

Table 5: T50% and T80% values of Tiagabine-SOLANUM MELONGA polymer bio-flexy films

Ratio	T50 % (hrs.)	T80 % (hrs.)
FSM1(1:1)	5.09	5.70
FSM2(1:3)	40.76	44.65
FSM3(1:5)	**3.70**	**4.12**
FSM4(1:6)	2.02	3.36
FSM5(1:10)	7.70	8.84

Table 6: T50% and T80% values of Tiagabine-Sodium CMC flexy films

Ratio	T50 % (hrs.)	T80 % (hrs.)
FS1(1:1)	**6.24**	**6.82**
FS2(1:3)	3.34	7.13
FS3(1:5)	3.53	7.22
FS4(1:6)	3.41	7.10
FS5(1:10)	3.67	7.29

Table 7: Kinetic Release of Tiagabine-SOLANUM MELONGA polymer bio-flexy films

Release Kinetics Analysis Dynamic Method Formulation of Tiagabine: Solanum melongena Bio-Flexy Films							
Formulations	**R^2**					**Best Fit Model**	**Mechanism of Action**
	Zero order	**1st order**	**Higuchi Matrix**	**Peppas**	**Hixon Crowell**		
FSM1 (1:1)	0.8815	0.8818	0.9314	0.9632	0.8817	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)
FSM2 (1:3)	0.8691	0.8692	0.9245	0.8613	0.8692	Higuchi Matrix	Anomalous Transport
FSM3 (1:5)	**0.9548**	**0.9550**	**0.9219**	**0.9770**	**0.9549**	**Peppas Korsmeyer**	**Fickian Diffusion (Higuchi Matrix)**
FSM4 (1:6)	0.8268	0.8274	0.9186	0.9645	0.8272	Peppas Korsmeyer	Fickian Diffusion (Higuchi Matrix)
FSM5 (1:10)	0.8596	0.8599	0.9347	0.9427	0.8598	Peppas Korsmeyer	Anomalous Transport

Table 8: Kinetic Release of Tiagabine-Sodium CMC 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**		
FS1 (1:1)	**0.8928**	**0.8929**	**0.9320**	**0.9641**	**0.8929**	**Peppas Korsmeyer**	**Fickian Diffusion**
FS2 (1:3)	0.8667	0.8673	0.9421	0.9602	0.8671	Peppas Korsmeyer	Fickian Diffusion
FS3 (1:5)	0.8548	0.8554	0.9442	0.9638	0.8552	Peppas Korsmeyer	Fickian Diffusion
FS4 (1:6)	0.8758	0.8763	0.9404	0.9650	0.8761	Peppas Korsmeyer	Fickian Diffusion
FS5 (1:10)	0.8841	0.8845	0.9351	0.9488	0.8844	Peppas Korsmeyer	Fickian Diffusion

DISCUSSION

In this study nanosized tiagabine loaded bio-flexy films were formulated and evaluated. The aim of research work is brain targeting of drug via oro-soft palatal mucosa to obtain systemic drug delivery and to explore the potentialities of soft palatal mucosa as a drug delivery platform. Biopolymer is used to prepare bio-flexy films because of its biodegradability, biocompatibility, non-toxic, non- irritant in nature and no reaction on soft palatal surface. Physicochemical characterization of biopolymer such as colour, odour, taste, texture and chemical tests were carried out. The isolated biomaterial was rich in protein, starch and carbohydrates. Biomaterial showed excellent film forming properties along with mucoadhesive and mucoretentive properties. Thus, biomaterial was suitable for preparing bio-flexy films for trans-soft palatal delivery. Drug polymer interaction was not observed because no change in wavelength of pure drug and drug to polymer ratio. The functional groups present in the bio-polymer were comparable to the groups present in the mucoadhesive polymers. Bio-flexy films were prepared by solvent casting technique which is the easiest and reproducible method to prepare flexy film without need of any sophisticated instruments. Drug to polymer ratio was chosen at five levels for **SOLANUM MELONGA**; FSM1 (1:1), FSM2 (1:3), FSM3 (1:5), FSM4 (1:6), FSM5 (1:10), and five levels for **Sodium CMC** FS1 (1:1), FS2 (1:3), FS3 (1:5), FS4 (1:6), FS5 (1:10). Prepared bio-flexy films of 1cm² were cut using a round punch for evaluation parameters and stability studies. SOLANUM MELONGA biopolymer was found to be **2.24±0.01%**. Surface thickness of films was in range of 0.019 mm to 0.076 mm. Folding Endurance was 86-114 indicating the flexibility of the bio-flexy films. Surface pH was found in range of 7.01±0.02 to 7.01±0.01which is in the range of physiological pH, so prepared formulations suitable for soft palatal formulation. Weight Uniformity ranged from 0.001±0.02 to 0.032±0.01. Formulations **FSM3** (containing Tiagabine: SOLANUM MELONGA biopolymer (1:5)) having **R^2=0.9770**, best fit model: peppas korsmeyer, follows Fickian diffusion (Higuchi matrix) release mechanism, T 50%: 3.70 hrs. , T80%: 4.12 hrs. and **FS1** (containing Tiagabine: Sodium CMC (1:1)) having **R^2=0.9641**, best fit model: peppas korsmeyer, follows **fickian diffusion** release mechanism, T 50%: 6.24 hrs., T80%: 6.82 hrs. were found to be best formulation as per release study using BITS Software 1.12. Stability study revealed stable bio-flexy films with no significant change in physical appearance and stable pH. Prepared formulations of tiagabine loaded bio-flexy films are suitable for soft palatal delivery.

Stability study revealed stable bio-flexy films with no significant change in physical appearance and stable pH. Biomaterial was isolated and characterized for formulation in order to achieve controlled release for prolonged time period.

CONCLUSION

In this research work, nanosized tiagabine loaded bio-flexy films were formulated using a novel biopolymer isolated from SOLANUM MELONGA pulp, and other co-processing agents. The performance of prepared formulations was evaluated in comparison to tiagabine-standard polymer (Sodium CMC) films. The purpose of study was to determine the feasibility of oro-trans soft palatal drug delivery platform, suitability of isolated biopolymer than standard polymer. Till date, anticonvulsant molecule delivery to brain is a significant challenging task so in this work, a novelistic attempt has been made to deliver anticonvulsant through Soft Palatal platform as it is enriched by rich blood and neural supply hence Bio-Flexy Films loaded with Tiagabine were formulated and screened for its performance. The results of all evaluation parameters revealed that controlled drug release can be achieved by this drug delivery route up to 48hrs. Formulation **FSM3** (containing Tiagabine: SOLANUM MELONGA biopolymer (1:5)) was selected as Best Film.

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Abbreviations

Abbreviations	Full Forms (Expanded meaning)
BBB:	Blood Brain Barrier
Sodium CMC:	Sodium Carboxyl Methyl Cellulose
FSM:	Bio-Flexy Film Formulation of Tiagabine with SOLANUM MELONGA biopolymer
FS:	Bio-Flexy Film Formulation of Tiagabine with Sodium CMC standard polymer
GIT:	Gastro Intestinal Tract
no.:	Number
U.V.:	Ultraviolet Visible Spectroscopy
cm^2:	Centimeters Square
mins:	Minutes
mm:	Millimeters
hrs. :	Hours
mL:	Milliliters
gm.:	Grams
Mg:	Milligram
rpm:	Revolutions per minute
KBr:	Potassium Bromide
Std.	Standard

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