

Design and Evaluation of Bio-Flexy Films using a Novel Biopolymer from *Manilkara zapota* Loaded with Nanosized Tiagabine

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Abstract

The aim of Research work was to formulate nanosized bio-flexy films using a novel biopolymer isolated from *Manilkara zapota* fruit pulp containing tiagabine as a model drug. The soft palate drug delivery helps bypass first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract gets avoided. Tiagabine, anticonvulsant drug possesses $t_{1/2}$: 7-9 hours (low); protein binding: 96%; water solubility: 22 mg/l enhances acts as selective GABA reuptake inhibitor. Side effects include abdominal pain, pharyngitis, suicidal thoughts and sudden unexpected death.

Biopolymer isolated from *Manilkara zapota* was used to prepare bio-flexy films because of its biodegradability, biocompatibility, non-toxic, non-irritant in nature and non-reactive on soft palatal surface. Physicochemical characterization of biopolymer displayed inbuilt properties of film ability, mucoadhesivity. Bio-flexy films were prepared by solvent casting technique. Drug to polymer ratio was chosen at five levels for *Manilkara zapota* FMZ1-FMZ5 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 *Manilkara zapota* biopolymer was found to be $28.236 \pm 0.02\%$. Thickness of formulated bio-flexy films was ranging from 0.029 mm to 0.041 mm, folding endurance: 85-100, 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, Formulation FMZ2 (containing Tiagabine: *Manilkara zapota* biopolymer (1:3)) was selected as Best Film as *in-vitro* release study results revealed prolonged duration of period, $R^2=0.9627$, peppas korsmeyer as best fit model, follows anomalous transport 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; Soft palatal delivery; *Manilkara zapota* biopolymer

Abbreviations: MZ: *Manilkara zapota*; Sodium CMC: Sodium Carboxyl Methyl Cellulose; FMZ: Bio-Flexy Film Formulation of Tiagabine with *Manilkara zapota* 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; Mg: Milligram; Rpm: Revolutions per minute; KBr: Potassium Bromide; Std: Standard

Introduction

Soft Palate (velum) is the soft tissue that is suspended from the posterior border of the hard palate. It is part of Oral mucosa, protects nasal passage, does not contain bone and provides improved absorption into blood stream as compared with oral administration to GIT. It is more convenient means of drug administration [1]. It has promising Non-keratinized histology with unique thickness. Surface area of the oral mucosa (200 cm^2) relatively small compared with the GIT ($350,000\text{ cm}^2$) and skin ($20,000\text{ cm}^2$).

Blood brain barrier (BBB) restricts entry of most drugs so Brain targeting of drugs to a specific site but also to retain it for the desired duration so as to elicit pharmacological action is a challenging task. Therapeutic potential of many drugs can be improved. Trans-Soft Palatal route offers a Novel Drug Delivery Platform for systemic delivery of drugs for Brain targeting [2]. It is well suited for a retentive drug delivery and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Palatal drug delivery 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. Blood supply to Soft palate is by Middle Meningeal artery; Accessory Meningeal artery; Greater Palatine branch of maxillary artery; ascending palatine branch of facial artery; ascending pharyngeal artery [2]. Soft palate is innervated by mandibular branch of trigeminal nerve (Cranial nerve V); Lesser palatine nerve; greater palatine nerve; nasopalatine nerve; glossopharyngeal nerve; motor nerves. When drug in nanosized form is administered by this route, then *via* inter and intra neural pathway, it can directly reach into brain by trigeminal nerve that connects soft palate to brain [3].

Epilepsy ranks 7th position causing 3.3% total deaths worldwide, that is expected to raise up to 6th position causing 3.7% of total deaths till year 2030. Antiepileptic drug tiagabine 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 *Manilkara zapota* pulp was incorporated to avoid toxicity that is by synthetic polymers. *Manilkara zapota* contains carbohydrates, glucose (5.84 to 9.23%), fructose (4.47 to 7.13%), sucrose (1.48 to 8.75%), total sugars (11.14 to 20.43%), starch (2.98 to 6.40%), tannins (3.16 to

6.45%) and sapotin [4]. Drugs directly enter the systemic circulation [5]. This route is non-invasive, non-mobile with highly mucoretention ability, afford high bioavailability, drugs directly enter the systemic circulation, lower doses, avoidance of the first-pass metabolism by the liver and metabolism by gastrointestinal tract. Thus to decrease dose frequency and to minimize adverse drug reactions, nanosized tiagabine loaded Bio-flexy films were suitably formulated that can provide sustained drug action up to 3-4 days.

Materials and Methods

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

POLYMERS: *Manilkara zapota* biopolymer (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.

Isolation of biomaterial from *Manilkara zapota*

250 gm of *Manilkara zapota* fruits were weighed and skin was removed. Slurry was prepared using 500 ml of distilled water, was filtered slurry using muslin cloth. To the filtrate, optimized quantity of propan-2-one was added in proportion of 1:2. In order to isolate biomaterial, kept the mixture in refrigeration for 24 hrs. The mixture was centrifuged at 3500 rpm for 15mins. The supernatant was separated while residue was collected. The biomaterial obtained was dried naturally, powdered, passed through sieve no.120, packed and stored for further use. The same procedure was repeated six times for optimization and % yield was calculated and reported.

Physicochemical characterization

The Physicochemical characterization of isolated bio-material was performed like colour, odour, solubility, melting point and various chemical tests were performed [5].

Test for carbohydrates: Molisch Reagent Test- 2 ml of biopolymer solution (0.1 gm dissolved in 2 ml of distilled water) was taken in a test tube. 2 drops of Molisch reagent (Solution of α -naphthol in 95% ethanol) was added. Solution was then poured slowly into a test tube containing 2 ml 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.

Test for proteins: Biuret Test- This test determines the presence of peptide bonds in protein content in the isolated biomaterial. 2 ml of biomaterial solution (0.1 gm dissolved in 2 ml 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.

Test for starch: 2 ml of biomaterial solution (0.1 gm dissolved in 2 ml 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).

Test for reducing sugar: 2 ml of biopolymer solution (0.1 gm dissolved in 2 ml of distilled water) was taken in a test tube. Added 1 ml each of Fehling's A (7 g $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ dissolved in distilled water containing 2 drops of dilute sulfuric acid) and Fehling's B (35 gm potassium tartrate, 12 gm of sodium hydroxide in 100 ml of distilled water). 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-exciptient interaction study

Drug-exciptient interaction study [5] 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-exciptient in the ratio of 1:1, 1:3 and 3:1 were taken in 3 different petri dishes. 1 ml of distilled water was added to wet the mixtures. Mixtures were then subjected to drying in oven for 30 mins at 50°C, followed by dilution with 2 ml 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-exciptient in the ratio of 1:1, 1:3 and 3:1 were taken in their physical forms (dry) in 3 different petri dishes. Mixtures were kept at room temperature for 2 hrs. followed by dilution with 2 ml of methanol. Ultraviolet Spectroscopy study was then performed. The shift in λ_{max} was reported in comparison to that of pure Tiagabine.

Spectral studies of isolated biopolymer

U.V. Spectroscopy: Determines λ_{max} , detection of functional groups, for qualitative as well as quantitative analysis. Shimadzu model 1800 has been used for UV analysis of the biomaterial. 10 mg of biomaterial was dissolved in 5 ml of distilled water. Distilled water was filled in both of the cuvette or in a reference cell for base line correction. When base line correction was made then one of the cuvette was replaced by filling biomaterial solution, distilled water has been used as a blank sample here. During scanning of the sample, a peak was observed which gives the maximum absorbance of the biomaterial. Thus the absorbance of the sample was recorded as a function of wavelength [5,6].

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: 1 mm Hg). The biomaterial was then analyzed by SEM [5,6].

IR Spectra: The physical form of isolated bio-material was solid so the KBr disc method was employed for IR spectroscopy, and in this technique about 1 mg of the solid sample was mixed with about 100 mg of pre dried and desiccated solid KBr. The mixture was finely ground in a mortar, preferably under an IR lamp to exclude any water vapors. The finely ground mixture was pressed under pressure of about 10 tons using a hydraulic pump to form a small pellet about 1-2 mm in diameter. The resulting KBr disc was removed from the KBr die and is positioned in a special holder into the path of the IR radiation and its spectrum was recorded within the range of 4000-200 cm^{-1} [5,6].

Conversion of Tiagabine Hydrochloride into Tiagabine by precipitation method

To 100 mg of tiagabine hydrochloride, 20 ml of distilled water was added in a test tube and shaken vigorously. Mixture was subjected to sonication for 1 cycle (each cycle of 3 mins) in ultrasonic bath sonicator. 10 ml of 1N sodium hydroxide solution was incorporated dropwise

in above Tiagabine solution. Precipitate was formed at bottom of test tube. Mixture was centrifuged for 15 mins at 3500 rpm. Tiagabine was separated, washed with 10 ml distilled water and air dried.

Preparation of standard curve of Tiagabine:

10 mg of tiagabine was dissolved in 30 ml of distilled water in a 100 ml volumetric flask and diluted up to the mark with distilled water (100 µg/ml). Dilutions of Concentrations (0.5, 1, 2, 3, 4 and 5 µg/ml) were prepared in 10 ml volumetric flasks. Volume was made up to 10 ml with distilled water ($\lambda_{max}=257$ nm). Absorbance was measured against solvent blank [6,7].

Nanosizing of tiagabine by novel method: 100 mg tiagabine was mixed with 10 mg dextrose, 5 mg fructose and 10 ml distilled water in mortar pestle and triturated. The mixture was transferred into beaker, sonicated for 5 cycles (3 mins/cycle in ultrasonic bath sonicator). Mixture was diluted with 50 ml 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 10 mg dextrose, 5 mg fructose and 10 ml methanol in mortar pestle and triturated. The mixture was transferred into beaker, sonicated for 5 cycles (3 mins/cycle in ultrasonic bath sonicator). Mixture was diluted with 50 ml 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 (Figure 1).

Formulation of bio-flexy films (solvent casting method)

Nanosized tiagabine (0.1 gm/100 ml) and *Manilkara zapota* 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) (10 mg/ml), fructose (5 mg/ml) were added and triturated. Added glycerine (10 µl) (plasticizer), pectin (3%) (Film Former). Distilled water (20 ml) was incorporated, uniformly triturated for 2 mins. Mixtures were subjected to magnetic stirring for 15 mins, followed by sonication for up to 5 cycles (each cycle 3 minutes). Mixtures were poured into petri dishes and kept for drying. Prepared films were removed from petri dishes by using 1% borax solution. Checked the film ability of prepared films (Table 1 and Table 2).

Evaluation of formulated bio-flexy films

Thickness: The thickness of randomly selected flexi film from every batch was determined using standard digital micrometer. The average thickness was determined and reported with appropriate standard deviation [8].

Folding endurance: Folding endurance of flexi film was determined by repeatedly folding one of the film at the same place till it broke or folded

Formulation	FMZ1 (1:1)	FMZ2 (1:3)	FMZ3 (1:5)	FMZ4 (1:6)	FMZ5 (1:10)
Tiagabine (mg)	100	100	100	100	100
<i>Manilkara zapota</i> 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 1: Formulation of Bio-flexy films using (*Manilkara zapota*) biopolymer.

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

Table 2: Formulation of Bio-flexy film using Sodium CMC as a synthetic polymer: Same procedure as *Manilkara zapota* was followed for formulation.

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.

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 flexi film was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 hour at room temperature. The pH was measured by bringing the electrode in contact with the surface of film and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate and avg. values were reported.

Weight uniformity study: Weight uniformity of flexi film determined by taking weight of ten flexy film of sizes 1 square cm diameter from every batch and weight individually on electronic balance. The average weight was calculated.

In-vitro drug release (by Modified M .S. Apparatus)

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 37°C using orbital shaker incubator. Samples were withdrawn at regular intervals ranging from 10 mins to 30 hrs. Complete Replacement of buffer each time. U.V. Spectral analysis was performed [9,10].

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°C ± 2°C and 45 ± 5% RH, 25 ± 2°C and 60 ± 5% RH and 2 ± 5°C temperature and RH values respectively. After every 15 days, the aggregation, nature, colour change, and *in-vitro* drug release of formulations was determined [11,12].

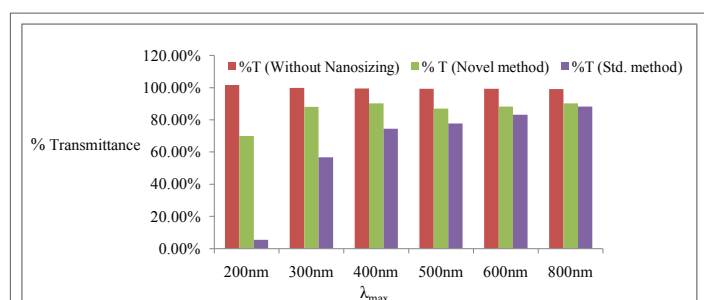


Figure 1: Comparative graph between % Transmittance and λ_{max} of pure Tiagabine (without nanosizing) with nanosized Tiagabine (by novel and standard methods).

Results

Isolation of biomaterial: The % yield for biomaterial from *Manilkara zapota* was found to be $28.236 \pm 0.02\%$.

Physicochemical properties of isolated biomaterial: The biomaterial obtained from pulp of *Manilkara zapota* was obtained in powdered texture that was brown in colour, characteristic odour and soluble in acetone. Colour Changing Point was found to be $186 \pm 2^\circ\text{C}$.

Drug Excipient Interaction Studies

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

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

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

Thus, no drug-excipient interaction occurred.

Colourimetry

Following reagents were used in colourimetry of Drugs: potassium permanganate, crystal violet, ferric chloride, iodine, potassium dichromate, methyl red, methyl orange, ferrous sulphate out of which potassium permanganate was found to be inert and showed No Interaction with Drugs. Drug showed brown colour with Potassium permanganate. Biomaterial showed different colour with different reagent. Drug and biomaterial colourimetry result showed drug is not entrapped. After performing the U.V. method, λ_{max} of drug-excipient mixture was found 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-flexyfilm.

Spectral studies of the isolated Bio-materials

IR Spectroscopy (using IRPal2.0 Software): The result of IR spectra of biomaterial isolated from *Manilkara zapota* showed the peak 3131 cm^{-1} , 1619 cm^{-1} , 1638 cm^{-1} , 1117 cm^{-1} , 1319 cm^{-1} which clearly indicated inbuilt mucoadhesive property with functional groups C=C-COOH, RCONH₂, RNH₂, RCOOH, S=O (Figure 2).

SEM analysis: It showed size range of biopolymer is $100\ \mu\text{m}$ (Figure 3).

Preparation of Calibration curve of drug: Calibration curve of Tiagabine was prepared in distilled water showed linearity. R² value was found to be 0.9311 (Figure 4).

Thickness of formulations: Thickness of nanosized tiagabine loaded bio-flexy films containing *Manilkara zapota* biopolymer (FMZ1-FMZ5) was in range of 0.029 mm to 0.041 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 85-100 for nanosized tiagabine loaded Bio-flexy films containing *Manilkara zapota* biopolymer (FMZ1-FMZ5). 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 *Manilkara zapota* biopolymer (FMZ1-FMZ5) 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 *Manilkara zapota* biopolymer (FMZ1-FMZ5) 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 FMZ2 (Bio-Flexy film containing Tiagabine: *Manilkara zapota* biopolymer in ratio of 1:3) (Figure 5 and Figure 6)

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 (Tables 3-6).

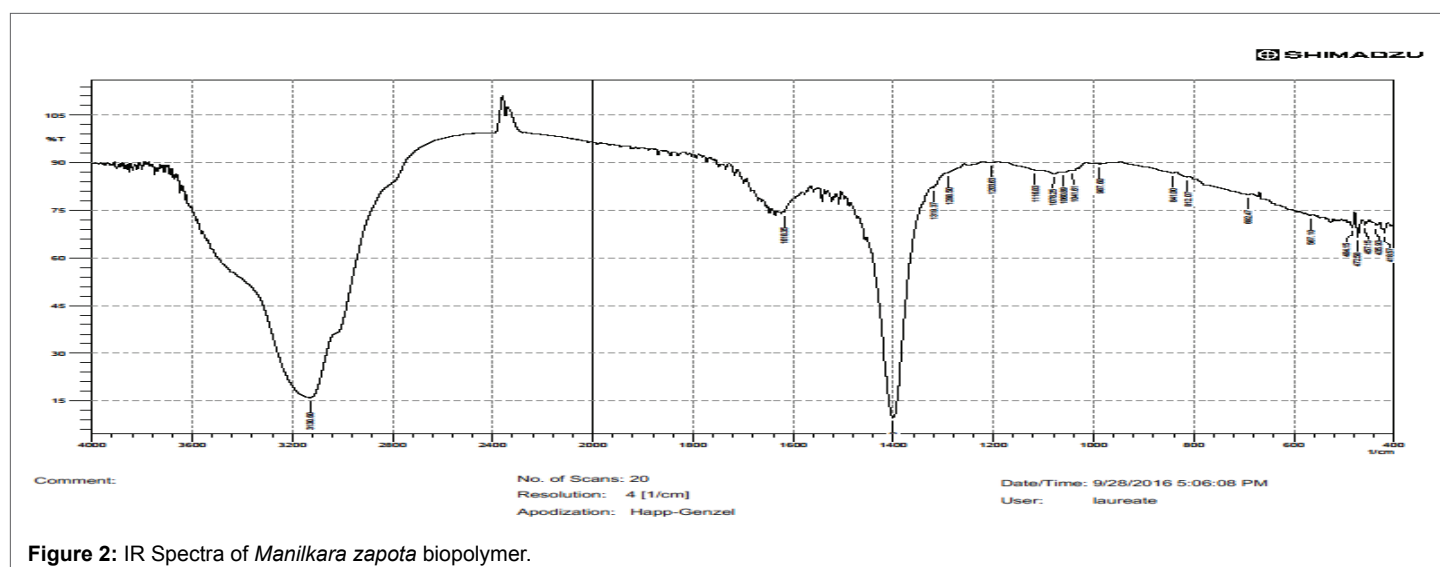


Figure 2: IR Spectra of *Manilkara zapota* biopolymer.

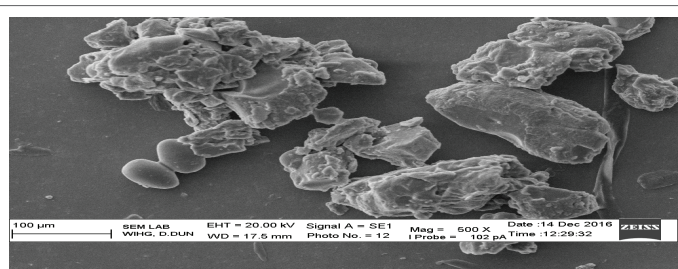


Figure 3: SEM of *Manilkara zapota* biopolymer.

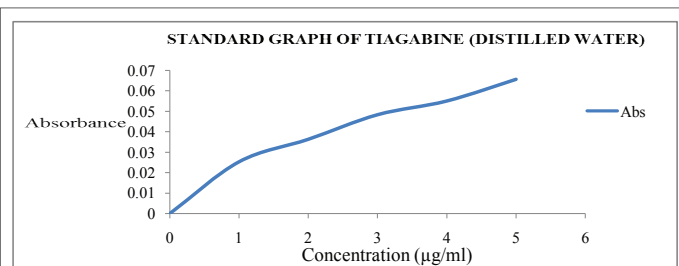


Figure 4: Standard curve of Tiagabine in distilled water.

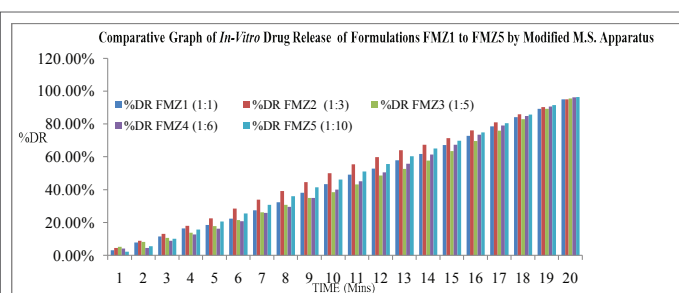


Figure 5: *In-vitro* drug release of tiagabine bio-flexy films using *Manilkara zapota* biopolymer by Modified M.S. Apparatus (dynamic method) (FMZ1-FMZ5).

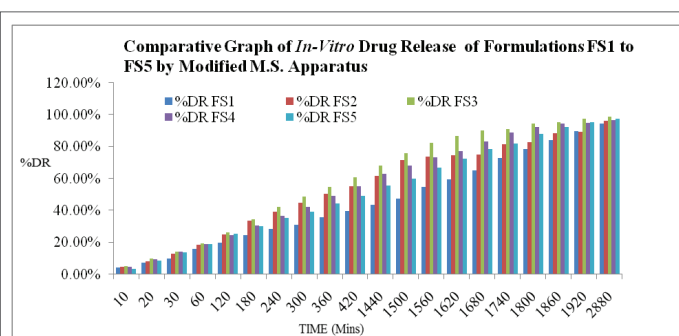


Figure 6: *In-vitro* drug release of Tiagabine bio-flexy films using Sodium CMC by Modified M.S. apparatus (dynamic method) (FS1-FS5).

Ratio	T50% (hrs.)	T80% (hrs.)
FMZ1 (1:1)	1.84	4.98
FMZ2 (1:3)	1.73	4.68
FMZ3 (1:5)	2.62	5.23
FMZ4 (1:6)	3.56	4.16
FMZ5 (1:10)	2.25	5.43

Table 3: T50% and T80% values of Tiagabine- *Manilkara zapota* polymer bio-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 4: T50% and T80% values of Tiagabine-Sodium CMC flexy films.

Discussion

In this study nanosized tiagabine loaded bio-flexy films were formulated and evaluated for targeting to brain *via* oro-soft palatal mucosa, a novelistic platform for systemic drug delivery. The rationale of study is to explore the potentialities of soft palatal mucosa as a drug delivery platform for brain targeting. Biopolymer is used to prepare flexy film 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 is rich in protein, starch and carbohydrates. Biopolymer was found non-toxic in nature. These biopolymers, so these are suitable for preparing flexi film for trans-soft palatal delivery. Drug polymer interaction was not observed because no change in wavelength of pure drug and drug to polymer ratio. These biopolymers were devoid of irritancy to soft palate because of its inertness, so these biopolymers were selected for formulating tiagabine bio-flexy films. The biopolymers showed excellent film forming properties along with mucoadhesive and mucoretentive properties. 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 *Manilkara zapota*; FMZ1 (1:1), FMZ2 (1:3), FMZ3 (1:5), FMZ4 (1:6), FMZ5 (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 1 cm² were cut using a round punch for evaluation parameters and stability studies. Percentage yield of *Manilkara zapota* biopolymer was found to be (28.236 ± 0.02 %). Surface thickness of films was in range of 0.029 mm to 0.041 mm. Folding Endurance was 85-100 indicating the flexibility of the bio-flexy films. Surface pH was found in range of 7.01 ± 0.02 to 7.01 ± 0.01 which 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 FMZ2 (containing Tiagabine: *Manilkara zapota* biopolymer (1:3)) having R²=0.9627, best fit model: peppas korsmeyer, follows anomalous transport release mechanism, T 50%: 1.73 hrs, T80%: 4.68 hrs and FS1 (containing Tiagabine: Sodium CMC (1:1)) having R²=0.9641, best fit model: peppas korsmeyer, follows fickian diffusion release mechanism, T50%: 6.24 hrs, T80%: 6.82 hrs were found to be best formulation as per release study. 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 achieved controlled release for prolonged period of time.

Conclusions

In this research work, nanosized tiagabine loaded bio-flexy films were formulated using a novel biopolymer isolated from *Manilkara zapota* fruit pulp, and other co-processing agents. Evaluated the performance of prepared formulations in comparison to tiagabine-standard polymer (Sodium CMC) films. The study aims to check and determine the feasibility of oro-trans soft palatal drug delivery platform and also suitability of isolated biopolymer than standard polymer. The results of

Release Kinetics Analysis Dynamic Method Formulation of Tiagabine: <i>Manilkara zapota</i> bio-flexy films							
Formulations	R ²					Best Fit Model	Mechanism of Action
	Zero order	1 st order	Higuchi Matrix	Peppas	Hixon Crowell		
FMZ1 (1:1)	0.7522	0.7525	0.9346	0.9566	0.7524	Peppas Korsmeyer	Anomalous Transport
FMZ2 (1:3)	0.736	0.7364	0.9365	0.9627	0.7362	Peppas Korsmeyer	Anomalous Transport
FMZ3 (1:5)	0.7661	0.7664	0.9328	0.9599	0.7663	Peppas Korsmeyer	Anomalous Transport
FMZ4 (1:6)	0.7726	0.773	0.9378	0.952	0.7728	Peppas Korsmeyer	Anomalous Transport
FMZ5 (1:10)	0.7355	0.7359	0.9358	0.9554	0.7358	Peppas Korsmeyer	Anomalous Transport

Table 5: Kinetic release of Tiagabine-*Manilkara zapota* polymer bio-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	1 st 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

Table 6: Kinetic release of Tiagabine-Sodium CMC Flexy Films.

all evaluation parameters revealed that controlled drug release can be achieved by this drug delivery route up to 48 hrs. Formulation FMZ2 (containing Tiagabine: *Manilkara zapota* biopolymer (1:3)) was selected as Best Film.

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