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# FORMULATION APPROACH FOR BROMOCRIPTINE DELIVERY IN NANO FORM *VIA* ORO-TRANS LABIO MUCOSAL ROUTE AND ITS PERFORMANCE EVALUATION

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**ABSTRACT:** The purpose of the current study was to formulate nanosized bromocriptine loaded mucoadhesive bio-flexy films using biopolymer from *Zea mays* for improved bioavailability and therapeutic efficacy *via* oro-trans labio mucosal route. Bromocriptine was nanosized by a novel method using 1,2,3-propanetriol as nanosizant. The biopolymer was isolated from *Zea mays* by treating the aqueous extract with an optimized quantity of non-aqueous solvent. Ten nanosized drug loaded films in different ratios (1:1, 1:2,1:3, 1:4 and 1:5) of biopolymer from *Zea mays* and Guar gum were prepared by "Solvent Casting Technique." Biopolymer from *Zea mays* and Guar gum was used as film former, 1,2,3-Propanetriol and D-glucose as flexicizer. All the films were evaluated using thickness, surface pH, folding endurance, weight and content uniformity, mucoadhesive, *in-vitro* drug release profile, *etc*. The isolated biopolymer was off-white in color, biodegradable and biocompatible. All films were thin, smooth, transparent to translucent in appearance and flexible in nature. All formulations adhered to the mucosal surface for more than 24 h. The amount of film former influenced the properties of different formulations. The formulation is having drug and biopolymer at a ratio of 1:2 (FZM2) showed the best performance with 180 times mucoadhesion time, 98.28% drug content uniformity, and release drug throughout 36 h. Due to the benefits of single daily dosing and reduced dose-related side effects, the novel formulation approach for bromocriptine delivery may act as a landmark for treatment and management of Parkinsonism, pituitary tumor, acromegaly, and type-II Diabetes mellitus.

**Keywords:** Biopolymer, Flexy films, Nanosizing, *Zea mays*

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**INTRODUCTION:** Parkinson's disease is the most prevailing degenerative neurological disorder which depletes striatal dopamine due to degeneration of dopaminergic neurons in substantial Niagra. Parkinson may remain for decades and reduces the quality of life in aged patients.

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The symptoms of Parkinson's disease are akinesia, bradykinesia, resting tremor, muscular rigidity, and disturbance in posture and walking [1].

Bromocriptine is widely used in Parkinson's disease. Bromocriptine is an ergot derivative and has been marketed for more than 20 years. It shows potent dopamine agonistic activity which stimulates postsynaptic dopamine receptors. Bromocriptine stimulates hypothalamic dopaminergic receptors resulting in an increase in prolactin inhibitor factor, decreasing secretion of prolactin from the anterior pituitary thus used in the treatment of hyperprolactinemia. Bromocriptine also decreases growth hormone production and

used in acromegaly [2]. In 2009 FDA approved QR-bromocriptine (Cycloset™) for the treatment of type-II diabetes mellitus [3]. The labial mucous membrane is highly vascularized, with enormous blood capillaries giving it a reddish color. The lower lip is supplied from the superior and inferior labial branches of the facial artery, one of the six non-terminal branches of the external carotid artery. The oro-labio mucosa is non-keratinized in nature and composed of stratified squamous epithelium. All muscles acting on the labium are supplied (motor supply) by the nerve of the second pharyngeal arch, the facial nerve ($7^{th}$ cranial nerve) [4-5]. The lower lip receives nerve supply from the mental nerve innervated by the mandibular branch of the facial nerve (*via* the inferior alveolar nerve) [6].

Mucoadhesive substances can adhere to the mucosal surface and retain there for a longer period. Bio-flexy films tend to do the same. Films are being manufactured by Solvent casting method and Hot-melt extrusion techniques utilizing a film former, plasticizers for flexibility, and stabilizers. These mucoadhesive patches and films have the convenience of ease of administration, flexibility, reduced dosing frequency because of longer retention time, rapid onset of drug delivery, dose accuracy, easy storage and handling, improved bioavailability, dose reduction due to improved bioavailability thus reduces dose-related adverse effects. Recently the mucoadhesive buccal strips are included in European Pharmacopoeia 7.4 which shows the confirmation of wide acceptability of these films as dosage form [7].

Corn is obtained from kernels of *Zea mays*, is an annual crop that belongs to the family of grasses, *i.e.* Poaceae and commonly known as maize, corn, and makka in Hindi. The kernels contain vitamin C, vitamin E, vitamin K, vitamin B1 (thiamine), vitamin B2 (niacin), vitamin B3 (riboflavin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), folic acid, selenium, N-p-coumaryl tryptamine, and N-ferrulyl tryptamine. Potassium is a major element present in it. The maize oil is a rich source of tocopherols, especially γ-tocopherol. Corn starch is well recognized for its uses in the food industry and pharmaceutical industries as diluent. Roasted corn kernels are used as coffee substitute [8-9].

In the present research work, oro-labio mucosal route is explored as a potential mucoadhesive drug delivery site for effective delivery of nanosized bromocriptine.

**MATERIALS AND METHODS:** Bromocriptine was received as a gift sample from Teva Czech Industries, Czech Republic. *Zea mays* were procured from the local market of Dehradun, Uttarakhand, India. Guar gum, D-glucose and all other chemicals and solvents were of analytical reagent grade.

**Isolation of Biomaterial from the Pulp of *Zea mays*:** 200 grams powder of *Zea mays* was taken, mixed with 250 ml distilled water and kept on mechanical stirrer at 4000 rpm for 1 h. Then it was centrifuged at 3000 rpm to remove the extraneous matter. The supernatant liquid was treated with the optimized quantity of propanone and kept in the refrigerator for 24 h. The isolated bio-material was separated by centrifugation at 4000 rpm for 25 min. The bio-material was dried in a desiccator for 48 h. The bio-material extraction was repeated 6 times & practical yield was reported [10].

**Physico-chemical Characterization and Spectral Analysis of the Isolated Bio-material:** The isolated bio-material was tested for various physico-chemical properties like colour,odor, solubility, color changing point, chemical tests for carbohydrates (molisch test, benedict's), proteins (biuret test) and starch, SEM analysis and spectral studies like I.R and Proton-NMR Spectra was performed using Shimadzu IR Tracer-100 [11].

**Drug Excipients Interaction Study:** The drug interaction study was performed by wet and dry method. The drug was physically mixed with excipients in dry method and in the wet method the physical mixture was treated with 2 ml of distilled water in the ratios of 1:1, 1:3 and 3:1 and kept for 3 days. Both the mixtures were dissolved in methanol and then analyzed by TLC and UV Spectrophotometric method at 245 nm [12].

**A Novel High through Put Screening Method for Determining the Nano Particle Size Range by Characterization by U.V Spectroscopic Method:** If drug particles were dissolved in nano level it shows an increase in % transmittance with a decrease in absorbance.

The increase in % T, which confirms that much % of the particle is falling above the selected range. The main principle involved in this method is when light passes through the solution, it shows 100% T with 0% absorbance in UV spectroscopy. In this method, nanosizing range of particles by U.V spectroscopy was evaluated after each cycle of sonication [13].

***Ex-vivo* Permeability Study:** Drug solution of 1mg/ml was prepared and 1ml drug solution added in the donor compartment. pH 7.4 buffer was prepared and was kept in the receptor compartment. Egg membrane was used as a biological membrane, and complete sample replacement was done every time.

**Formulation of Nanosized Bromocriptine loaded Flexy Films**: Bromocriptine was nanosized by using 1,2,3-Propanetriol as nanosized [14]. Biopolymer from *Zea mays* and guar gum was accurately weighed in different ratios, *i.e.* 1:1, 1:2, 1:3, 1:4 and 1:5 as shown in **Table 1** and triturated with 10 µl of 1,2,3-Propanetriol, and 80 mg of D-glucose as flexicizer. 10 ml of distilled water added into it and subjected for mechanical stirring at 2000 rpm for 30 min. 10 mg of nanosized drug was dissolved in 5 ml of methanol. The nanosized drug solution was added to the polymeric solution under mechanical stirring at 4,500 rpm. The resulting solution was spread on Petri dish having 5 cm diameter for natural drying of about 24 h and stored [10].

**TABLE 1: FORMULATION TABLE OF BROMOCRIPTINE LOADED FLEXY FILMS OF *ZEA MAYS* AND GUAR GUM**

| Formulation | FZM1 (1:1) | FZM2 (1:2) | FZM3 (1:3) | FZM4 (1:4) | FZM5 (1:5) | FGG1 (1:1) | FGG2 (1:2) | FGG3 (1:3) | FGG4 (1:4) | FGG5 (1:5) |
|---|---|---|---|---|---|---|---|---|---|---|
| Bromocriptine (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| *Zea mays* (mg) | 1% | 2% | 3% | 4% | 5% | - | - | - | - | - |
| Guar gum (mg) | - | - | - | - | - | 1% | 2% | 3% | 4% | 5% |
| D-glucose (mg) | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| 1,2,3-Propanetriol (µl) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Distilled Water (ml) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**Evaluation of Nanosized Bromocriptine Loaded Flexy Films:**

**Appearance, Weight Uniformity, and Content Uniformity Study:** All the flexy films were weighed three times, then weight uniformity was calculated. All formulated flexy films were evaluated for its drug content uniformity. Selected film (1 $cm^2$) was transferred into a 100 ml volumetric flask containing 7 ml of phosphate buffer of pH 7.4 and 1 ml of methanol. The contents of the flask were stirred for 4 h on a magnetic stirrer. The drug content was then determined after appropriate dilutions by using a UV spectrophotometer (Shimadzu 1800) [12].

The drug content was calculated by using the below equation:

Drug content = (Analyzed content/Theoretical content) × 100 ….. (Eq1)

**Folding Endurance and Surface pH:** The selected films were subjected repeatedly folding the film (of area 2 $cm^2$) at the same place until it broke and the numbers of folding recorded. The surface pH of flexy films was measured by using pH meter [12].

**Mucoadhesion Study using the Shear Stress Method:** The adhesive property of the prepared films was determined by *in-vitro* shear stress method. Films were placed between two glass plates and subjected to shear stress for assessment of *in-vitro* adhesive strength using weight required for breaking adhesive bonds between the material and the glass plate after a specified contact time of 5, 10, 15 and 30 min [15].

**Mucoadhesion Study using the Rotating Basket Method:** The mucoadhesive property of prepared films was evaluated by Rotating basket method using Type II Dissolution apparatus *Capra aegagrus* (goat) intestinal mucosa. The fresh intestinal mucosa was attached over the cylindrical basket. The prepared flexy films adhered to the membrane with gentle pressing. Then the cylinders were rotated at 100 rpm in 900 ml of phosphate buffer pH 7.4 at 37 ± ºC. After each 30 min and up to 48 h the strip was observed for any dislodgement or disintegration from the mucosal surface. The results were compared with the standard films of Guar gum [15].

***In-vitro* Drug Release Study:** The *in-vitro* drug diffusion was carried out by using the Dynamic Franz diffusion cell method. Eggshell membrane was tied on the donor compartment, and flexy film of 1 $cm^2$ area was kept on the above the membrane and the receiver compartment was filled with 7 ml of phosphate buffer pH 7.4. 4 ml of sample was withdrawn at the intervals of 0, 10, 20, 30, 60, 120, 180, 300, 360, 480 and1440 min and replaced with 4 ml of fresh medium. The amount of drug released was assessed by measuring the absorbance at 245 nm using UV spectrophotometer (Shimadzu 1800) [12].

**Stability Study:** Optimized best flexy strip was subjected to stability study as per ICH guidelines. The films were kept in an incubator (stability study chamber) maintained at 37 ± 5 °C and 75 ± 5% Rh for 6 months. The change in appearance, physical characteristics, and release behavior of the stored films were investigated from 0-6 months [16].

## RESULTS AND DISCUSSIONS:

**Physico-Chemical Characterization and Spectral Analysis of the Isolated Bio-Material:** The % yield of *Zea mays* was found to be 4.02 ± 0.23%. The isolated biomaterial was carbohydrate and proteinaceous. The physicochemical characterization is shown in **Table 2** and **3**.

**TABLE 2: PHYSICAL CHARACTERIZATION OF BIO-MATERIAL**

| | |
|---|---|
| Color | Off-white |
| Odor | Odorless |
| Taste | Characteristic |
| Solubility | Soluble in water, insoluble in isobutyl alcohol and chloroform |
| Melting Point | 220 ± 5 ºC |

**TABLE 3: CHEMICAL CHARACTERIZATION OF BIO-MATERIAL**

| S. no. | Test | Observation | Inference |
|---|---|---|---|
| 1 | Molisch | + | Carbohydrate present |
| 2 | Benedict | + | Carbohydrate present |
| 3 | Fehling's | + | Carbohydrate present |
| 4 | Biuret | + | Proteins present |
| 5 | Ninhydrin | + | Proteins present |

The bio-material was purified by hot dialysis method, and it was devoid of chlorides and sulfates. The functional groups of bio-material were elucidated by I.R. spectral studies. The I.R. spectral interpretation by IR Pal V 2.0 reported the presence of 3232 $cm^{-1}$ (O-H stretching hydroxyl), 1627 $cm^{-1}$ ($RCONH_2$), 1575 $cm^{-1}$ (C-O stretch), 1439 $cm^{-1}$ (Ar C-C stretch), 1291 $cm^{-1}$ (RCO-OH or RCOOR), 1168 and 1001 $cm^{-1}$ (thiocarbonyl), 932 $cm^{-1}$ (RCO-OH), 757 and 718 $cm^{-1}$ (ortho-disub. /monosubst./meta-disubstitution) **Fig. 1**. These functional groups confer mucoadhesive property to the biopolymer.

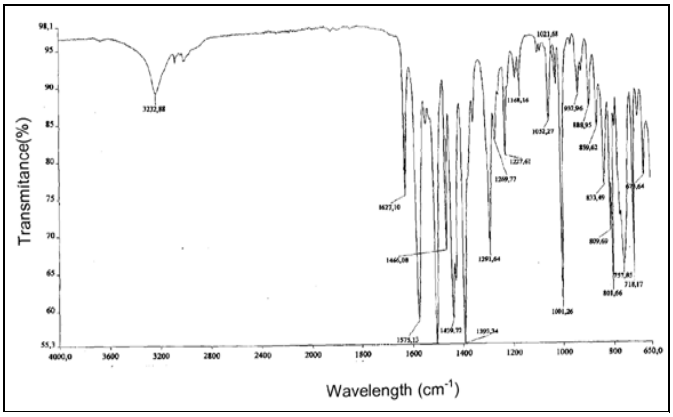


**FIG. 1: IR SPECTRA OF BIOPOLYMER ISOLATED FROM *ZEA MAYS***

Proton-NMR spectra of biopolymer depicted the presence of possible groups of hydrogen atoms attached to different functional groups *viz*. $RCH_3$ (chemical shift at 0.8477ppm), $RCH_2R$ (at 1.2535ppm), $RCH_2NH_2$ and $ArCH_3$ (at 2.4987 and 2.5165ppm), RC(triple bond) CH (at 2.9891ppm), $RCH_2I$ (at 3.1094 and 3.2969ppm), $RCH_2Br$ (at 3.4787ppm) **Fig. 2**. Allylic signals routinely appear when carbonyls (ketones, esters, aldehydes, acids, amides) or alkenes or aromatics are present. Oxygenated sp3 –carbons are routinely present when functional groups that contain single oxygen bonds like alcohols, ethers, or esters.

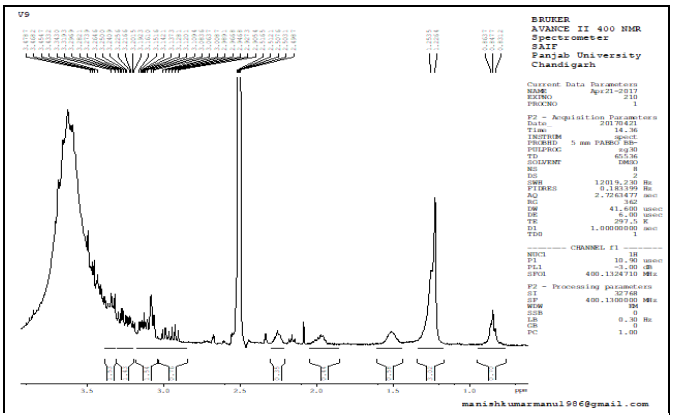


**FIG. 2: 1H-NMR SPECTRUM OF BIOPOLYMER ISOLATED FROM *ZEA MAYS***

DSC analysis measures the amount of heat absorbed when the temperature of the sample is raised at a linear rate. The DSC Curve depicts an

endothermic peak at 107.30 ºC; it is melting point of biomaterial and also shows a monotropic transition, *i.e.* solid-solid transition than a modification just formed melts. The on-set temperatures, 68.33 °C on heating and 128.92°C on cooling are very far having an area of 6115.723mJ **Fig. 3**.

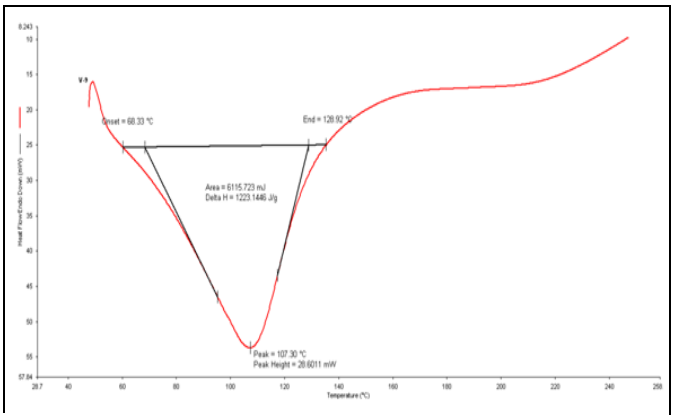

**FIG. 3: DSC CURVE OF BIOPOLYMER ISOLATED FROM *ZEA MAYS***

**Drug Excipients Interaction Study:** The studies revealed that there was no interaction between the drug and the formulation excipients. The same was confirmed by the result of the thin layer chromatography and UV spectroscopy in which no change was seen in the Rf value and ƛ max and absorbance respectively. And it was used for formulations.

**Nanosizing Characterization by U.V Spectroscopic Method:** Nanosized particles were evaluated by measuring % Transmittance before and after each cycle of sonication.

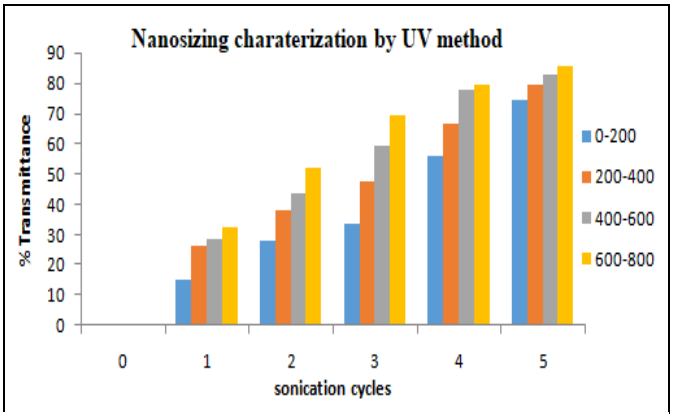


**FIG. 4: NANOSIZING CHARACTERIZATION BY UV SPECTROSCOPIC METHOD**

As the number of sonication cycles was increased, there was an increase in the % transmittance, indicating that the particles may be gone in the nano range, thus increasing the transmittance **Fig. 4**.

***Ex-vivo* Permeability Study:** Drug permeability was assessed by using the eggshell membrane as a biological membrane. A permeation graph was plotted between concentrations vs. time, depicting the amount of drug permeated through the membrane **Fig. 5**.

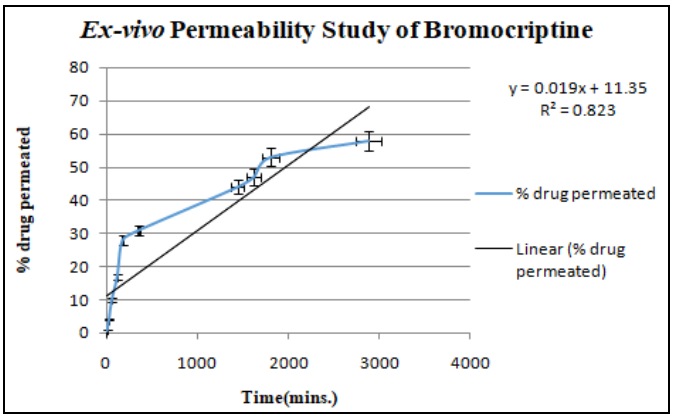


**FIG. 5: *EX-VIVO* PERMEATION STUDY OF BROMOCRIPTINE**

**Formulation of Nanosized Aripiprazole Loaded Flexy Films:** Ten nanosized aripiprazole loaded bio-flexy films (FZM1-FZM5 and FGG1-FGG5) were prepared by using biopolymer isolated from *Zea mays* as a mucoadhesive film former, Guar gum as standard mucoadhesive polymer, D-glucose as flexicizer and other co-processing agents like 1,2,3-Propanetriol as a plasticizer. All the prepared formulations were subjected to different evaluation parameters.

**Evaluation of Nanosized Aripiprazole Loaded Flexy Films:** All flexy films were transparent, smooth and translucent in appearance, thin, and flexible. The weight variation and % drug content of all the flexy film were ranged from 30.48-36.51 mg and 98.8-99.4%, respectively, as depicted in **Table 4**. All the prepared formulations showed folding endurance from 120 times to 161 times, as shown in **Table 4**.

Folding endurance study explains that there was an increase in the flexibility of the films as the polymeric concentration was increased in the formulations. FGG5 showed maximum folding endurance of 161 times in comparison to other formulations; this may be due to the presence of the

highest concentration of polymer and optimum concentration of flexicizer. FZM1 showed minimum folding endurance, which is comparable with FGG1 in the same concentration ratio. All the prepared films have surface pH in the range of 7.34 to 7.40, as shown in **Table 4**.

**TABLE 4: SURFACE pH, WEIGHT UNIFORMITY, PERCENT DRUG CONTENT AND FOLDING ENDURANCE OF ARIPIPRAZOLE LOADED FLEXY FILM FORMULATIONS**

| Formulation code | Surface pH | Weight uniformity (mg) | % Drug content | Folding endurance (times) |
|---|---|---|---|---|
| FZM1 | 7.35 ± 0.03 | 31.33 ± 0.06 | 98.8 ± 0.04 | 120 ± 05 |
| FZM2 | 7.34 ± 0.04 | 34.54 ± 0.10 | 99.2 ± 0.06 | 129 ± 03 |
| FZM3 | 7.39 ± 0.03 | 33.98 ± 0.08 | 99.4 ± 0.05 | 143 ± 02 |
| FZM4 | 7.34 ± 0.04 | 36.51 ± 0.07 | 99.3 ± 0.07 | 149 ± 04 |
| FZM5 | 7.40 ± 0.05 | 36.68 ± 0.09 | 98.7 ± 0.05 | 158 ± 04 |
| FGG1 | 7.38 ± 0.03 | 30.48 ± 0.09 | 98.9 ± 0.04 | 122 ± 05 |
| FGG2 | 7.36 ± 0.05 | 32.57 ± 0.08 | 98.9 ± 0.03 | 129 ± 05 |
| FGG3 | 7.39 ± 0.04 | 34.88 ± 0.11 | 99.1 ± 0.06 | 141 ± 03 |
| FGG4 | 7.41 ± 0.05 | 35.96 ± 0.10 | 99.2 ± 0.05 | 150 ± 02 |
| FGG5 | 7.38 ± 0.03 | 36.18 ± 0.07 | 98.8 ± 0.04 | 161 ± 03 |

***In-vitro* Mucoadhesion Study:** The mucoadhesion of the prepared films was assessed by Shear stress and *in-vitro* Rotating basket method using goat intestinal mucosa **Fig. 6**.

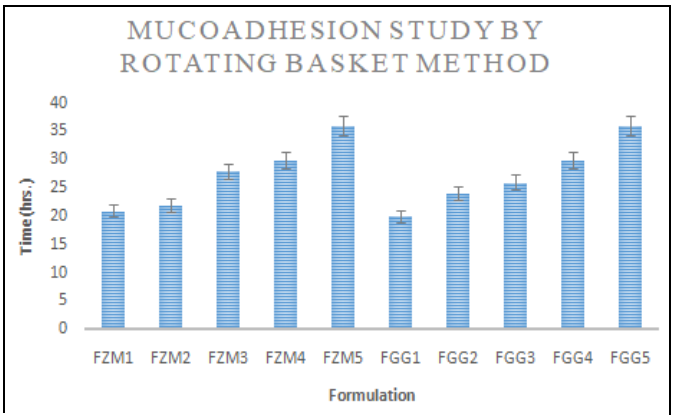


**FIG. 6: *IN-VITRO* MUCOADHESION STUDY BY ROTATING BASKET METHOD**

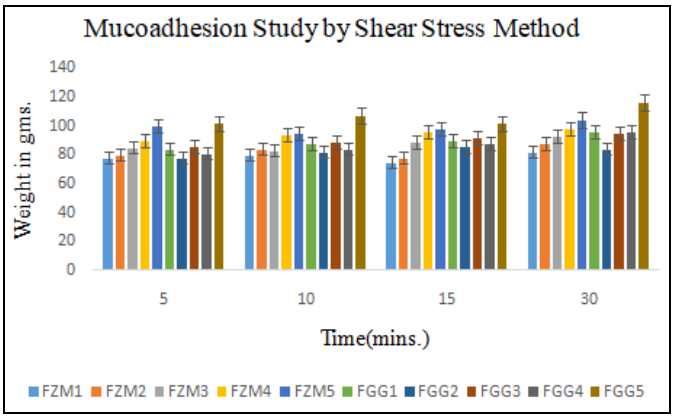


**FIG. 7: *IN-VITRO* MUCOADHESION STUDY BY SHEAR STRESS METHOD**

The *in-vitro* muco-adhesion study showed that formulation FZM5 and FGG5 had maximum mucoadhesion time of 36 h. FZM1 and FGG1 showed least mucoadhesion time of 21 and 20 h respectively. This may be due to the minimum concentration of biopolymer. Upon increasing the biopolymer and standard polymer concentration, there was an appreciable increase in the mucoadhesion time. All the films showed good mucoadhesive strength in Shear Stress Method. As the concentration of polymeric substance was increased, there was a proportional increase in mucoadhesive strength also. The polymeric substance has various hydrogen bond forming groups (*e.g.*, hydroxyl, carboxyl groups) which confers the most promising mucoadhesivity **Fig. 7**.

***In-vitro* Drug Release Study:** The *in-vitro* drug release kinetics was analyzed by BIT-SOFT 1.12. The t50% and t80% of formulations were calculated and reported.

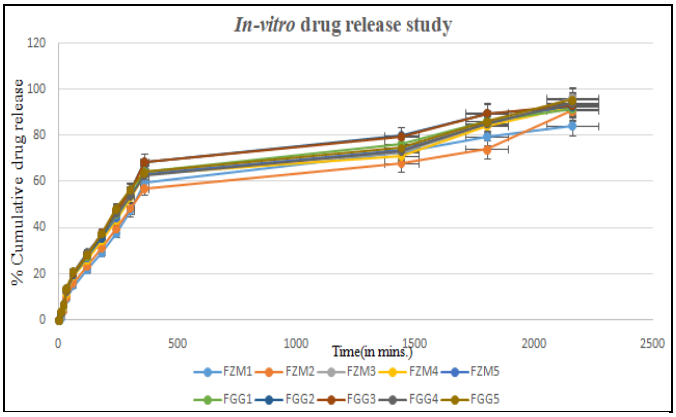


**FIG. 8: *IN-VITRO* DRUG RELEASE STUDY BY FRANZ DIFFUSION CELL APPARATUS**

The comparative drug release profile of all the formulations showed that the drug released followed the descending order: FZM1>FZM2>

FGG1>FGG2>FZM4>FGG3>FZM5>FGG4>FGG 5>FZM3 **Fig. 8**. The *in-vitro* drug release study revealed that formulation FZM3 have t50% and t80% of 4.5 h and 28 h respectively and released 72.656% of the drug in 24 h. Formulation FZM3 followed Higuchi-Matrix Model with $R^2$ value 0.9310 and mechanism of drug release was Anomalous Transport as shown in **Table 5**.

**TABLE 5: MODEL FITTING FOR FORMULATION FZM3 BY BIT-SOFT 1.12**

| FZM3 | |
|---|---|
| Model Fitting | $R^2$ |
| Zero-order | 0.7776 |
| 1st order | 0.8946 |
| Higuchi Matrix | 0.9310 |
| Peppas Korsmeyer | 0.9144 |
| Hixon Crowell | 0.8955 |

**DISCUSSION:** The isolated biopolymer is economical, safe, and devoid of any toxicity, and it can be further used as bio-film former in pharmaceutical formulations. The surface pH of all the formulations was near to oro-labial mucosal pH and devoid of any irritation as formulations contain a biopolymeric substance which is edible, biocompatible, economical and devoid of any mucosal irritant groups. Folding endurance study explains that there was an increase in the flexibility of the films as the polymeric concentration was increased in the formulations.

All the formulations showed significant mucoadhesion time, and as the proportion of polymer was increased, there was a proportional increase in the mucoadhesion time.

Bio-flexy films showed mucoadhesive property this may be due to the presence of mucoadhesive functional groups like carboxylic and hydroxyl in the biopolymer and its optimized concentration. Biopolymer showed drug release retardation property and released bromocriptine for a period of 36hrs, thus reducing the dosing frequency. Formulation FZM3 was selected as best optimized formulation on comparing its performance for different evaluation parameters *viz*. texture, flexibility, surface pH, weight uniformity, content uniformity, folding endurance, mucoadhesive, *in-vitro* drug release readability. The best formulation was stable over 6 months as there was no change in the physical appearance, drug content, and *in-vitro* release.

**CONCLUSION:** In the proposed research, mucoadhesive bio-flexy films based on nanosized bromocriptine and biopolymer from *Zea mays* were developed which showed good mucoadhesive property and released the drug for 36 h. The isolated biopolymer from *Zea mays* can serve as a film former and safe, biodegradable, biocompatible in nature; can be used for designing of various bioadhesive dosage forms. Nanosizing offers a reduction in particle size, thus improves the bioavailability of bromocriptine. Our results suggest that this formulation approach can be a potential dosage form for improved therapeutic efficacy and reduced dose-related adverse effects of bromocriptine through oro-trans labio mucosal route. Oro-trans labio mucosal route seems to be an effective and probably safe administration route for bromocriptine.

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**CONFLICT OF INTEREST:** The authors declare no conflict of interest.

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