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Development and Evaluation of Nanosized Risperidone Loaded Mucoadhesive Bioflexi Film by using biopolymers of Psidiumguajava (Guava) and Musaacuminata (Banana) for Oro Trans Soft Palatal Delivery

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KEYWORDS
Risperidone, Psidiumguajava, Musaacuminata, bioflexy, orotranspalatal.

ABSTRACT:
Formulation and evaluation of nanosized risperidone loaded mucoadhesive bio-flexy films using novel biopolymer isolated from Psidium guajava and Musa acuminata for schizophrenia treatment, by using orotranssoft palatal route. Trans soft palatal delivery system is an attractive approach for drug delivery system possess advantages as a bypass of the first-pass metabolism, prevent from digestive enzymes and rapid action of suitable drugs. The isolated biopolymer was subjected to various physicochemical characterization procedures. Risperidone was nanosized using sonication methods. Nanosized risperidone loaded bio-flexy films containing isolated Psidium guvaja and Musa acuminata biopolymers were prepared by Film Solvent Casting Technique. Formulations containing different ratios of drug and polymers using Optimized quantity of Dextrose. Evaluation parameters for biopolymers and bioflexy films were performed as Thickness, Folding Endurance, Surface pH, Weight Uniformity, Percentage Moisture Uptake (PTU), in vitro release etc. The bio-flexy film prepared using risperidone: Musa acuminata biopolymer in ratio of 1:5 and risperidone:Psidium guajava biopolymer in ratio of 1:5,both were taken as Best film.Prepared formulations of risperidone loaded bio-flexy films containing biopolymers were appropriate for Soft Palatal Delivery as it showed significant drug release due to its bio-polymeric nature.

Introduction

Soft palate region is present at the later side of mouth cavity. This region starts at its junction with the hard palate region and spread between the nasopharynx and Oropharynx to end its uvula which is present at inferior side. Its direction downwards from the hard palate with a concavity, which is placed at anterior side. It is usually a fold of a mucous epithelial membrane but that fold also bound to a wide aponeurosis attached to muscular tissue [1]. An absorbance and permeability surfaces of oral soft-palatal mucosal region is almost 4 - 4000 times high in comparison of a skin and thickness of the soft palatal site is around 156-223 um. Soft palatal mucosal membrane is one of the best recommended sites for trans mucosal absorption to explore and search the different medicaments distribution in an exact and systemic way. The Oral epithelial tissue of soft palatal is fully enclosed and consistently connects with non-keratinized squamous epithelial which is around 25-30 layer thick and thus speciously enhance mucoadhesivity. [2]The feature of soft palatal region, particularly the frontal partial region is completely supplying the seromucous glands, and marginal mark with fats containing tissue. The role of

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gland provides moisturization to the soft palatal opening to promote an adhesion property via excessive release of saliva from salivary glands. This glandular release may function as per a glandulous lubrication for reducing the frictional effects. The soft palate is mobile region, made up by muscle tissues which is bounded by mucous membrane. This is mainly accountable for closing of nasal airway region through process of engulfing, and similarly responsible for closing a nasal airway. At the time of sneezing, it helps to defend nasal passage via redirecting portion of excreted material from mouth. This drug delivery system provides ease administration of a drug. This route of drug delivery also Avoids first pass metabolism. It permits local insertion of tissue permeability, reduce the enzymatic activity or inhibit the hypersensitive immunologic response, therefore selective and preferable utilization of therapeutic agents like protein and peptide therapeutics and ionized nature of the drug can be easily achieved. Soft palatal route is an effective route for those drugs which show poor bio availability from oral route. Risperidone was firstly developed by a Jensen-Silag. It is an antipsychotic drug exhibit dopaminergic and serotonergic activity. Risperidone is a comparatively new antipsychotic medicine available globally from early 1990s. It is represented as unconventional, but it shows some of effectivity against an extrapyramidal side effect of antipsychotics disorder, when use drug quantity at high doses.[3,4]

MATERIAL& METHODS

Risperidone was obtained as a gift sample from Gentech Healthcare,Delhi.The natural biopolymers were extracted from **Psidium guajava (Guava) and Musaacuminata (Banana)**and the natural sources were procured from the market.

Isolation of biopolymer from the Fruits

500gm pulp from the sources was washed gently and ground in grinder for make a paste after that 200ml of distilled water was added in it and make a thick slurry & placed it in refrigerator for 24 hrs, allow it for sediment. The supernatant of slurry was taken & centrifuged a supernatant layer at 3000rpm for15 minutes. After centrifugation, the supernatant layer was taken and treated with acetone (1:2). The treated mixture was placed in refrigerator for 8 hrs. The mixture was processed under a centrifugation process at 3000rpm for 15 minutes and collected the sediment layer. After that dried a sediment layer naturally and spreading it on glass plate for 24hrs. Then dried biomaterial was screened through # 120 and stored in container. Then calculate a percentage yield and reported.

Physicochemical Characterization of Biopolymers-

A Physiochemical characterization of biopolymers was performed for the determination of several physical and chemical properties like colour, odour, solubility, melting point and various chemical tests were performed. Solubility was determined in different solvents (chloroform, dichloromethane, methanol, distilled water, acetone, carbon tetrachloride etc).

i) Test for carbohydrates

a. **Molisch Reagent Test:** this test was used to identify a carbohydrate presence in Biopolymers. In which Molisch reagent is used and treated with concentrated sulfuric acid was added slowly in few drops from the side of the test tube and observed reddish brown precipitates for its confirmation.

b. **Fehlings Test:** In this test the polymeric solution was treated with Fehling's reagent A and B solution in equal quantity and was then boiled and observed for colour change from green to yellow to orange to red.

ii) **Test for proteins**

a. **Ninhydrin Test:** In this test the polymeric solution was treated with 0.1% ninhydrin solution and was then boiled and cooled and observed for blue colour.

b. **Biuret test:** In this test take 2 mL of Biopolymer aqueous solution in test tube, then add 1 mL of 1% NaOH solution was added. Then add 1% Copper (II) Sulphate solution was in it, drop wise followed by continuous shaking and hold test tubes in stand allowed for 5 minutes. If any color change was observed in a mixture, reported it.

iii) **Test for starch:** Biopolymer were tested for starch using 1-2 drops of iodine solution and observed for appearance of purple colour.

iv) **Test for reducing sugar:** The presence or absence of reducing sugars was reported by adding the Fehling solution A and B to the bio-polymeric solutions.

Drug Excipients interaction study

Drug interaction study was performed by taking three different proportion of drug and bio-material 1:1, 1:3

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(3), 1105-1113 | ISSN:2251-6727

and 3:1 (i.e., for 1:1 ratio 10mg of drug and 10mg of biopolymer is used). The U.V absorbance of the three ratios was taken and compared with the absorbance of pure drug.

Wet method: In this method drug-excipients in the ratio of 1:1, 1:3 and 3:1 was taken separately in the Petri dish and then it was wetted with water, after that it was dried in the oven for 30 minutes then it was diluted with methanol and spectral study was performed by U.V spectrophotometry and after it was reported for presence or absence of shift it in the lamda max, in comparison to of the pure drug.

Dry method: In this method drug-excipients in the ratio of 1:1, 1:3 and 3:1 was taken in their physical forms (dry) in the separate Petri dish and put it at room 37°C for 48 hours then it was diluted with methanol and spectral study was performed by U.V. and it was reported for presence or absence of shift it in the, lamda max in comparison to of the pure drug.

Calibration Curve of Risperidone

The various quantity of a drug was prepared in the 6.8 and 7.4 pH phosphate buffer solution. Then the absorbance of each concentration at the maximum wavelength found after the scanning. The procedure was repeated thrice.

Nanosizing of Risperidone by Sonication method

By Novel method: 100 mg of drug 10mg of nanosizant (Dextran and PVA) were taken in a mortar pestle in geometrical progression: then added 10ml of distilled water slowly in it and continuously triturated it. The resultant mixture was stirred by a magnetic stirrer for 20 minutes. It was sonicated for 45 cycles (1 cycle allow for 3 minutes). Then resultant solution was subjected to micro centrifuge After that, the supernatant layer and the sediment layer were separated. Both resultant solutions Were evaporated and dried the nanoparticles were recovered and stored.

Preparation of Bioflexy Film

10 mg of Nanosized risperidone was triturated with biopolymer from Gauva(0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 4%, 5%, 6%, 7%) (Mucoadhesive, film forming cum biostabilizer) for 2 minutes using pestle mortar. Added 10 mL of Distilled Water (Solvent). To this dispersion, incorporated 100 mg of Dextrose (Flexicizer), with continuous stirring. Mixture was further uniformly triturated for 5 minutes. Made up the volume up to 30 ml by distilled water. Mixture was subjected to magnetic stirring for 15 minutes, followed by sonication for up to 5 cycles (each cycle 3 minutes). Clear dispersion obtained was poured into petridish and put it for drying at 37°C for 24 hours, placed it for a completion drying process. After that layer was removed carefully from a petridish. **(Table 1).**Similarly, ten various formulations of nanosized Resperidone with isolated biopolymer from banana in different ratios of 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:4, 1:5, 1:6 and 1:7 were prepared**. (Table 2)**

Figure 1: Preparation of Bioflexy films

Journal of Chemical Health Risks

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JCHR (2023) 13(3), 1105-1113 | ISSN:2251-6727

Table 1: Nanosized risperidone loaded bio-flexi films by using Psidium guajava

Formula	Drug (Risperidone) (mg)	Dextrose (mg)	Polymer: psidium guajava (mg)	Water (ml)
RG1(1:0.5)	10	100	50	20
RG2(1:1)	10	100	100	20
RG3(1:1.5)	10	100	150	20
RG4(1:2)	10	100	200	20
RG5(1:2.5)	10	100	250	20
RG6(1:3)	10	100	300	20
RG7(1:4)	10	100	400	20
RG8(1:5)	10	100	500	20
RG9(1:6)	10	100	600	20
RG10(1:7)	10	100	700	20

Table 2: Nanosized risperidone loaded bio-flexi films using Musa acuminata biopolymer

Formula	Drug (Risperidone) (mg)	Dextrose (mg)	Polymer: Musa acuminata(mg)	Water (ml)
RB1(1:0.5)	10	100	50	20
RB2(1:1)	10	100	100	20
RB3(1:1.5)	10	100	150	20
RB4(1:2)	10	100	200	20
RB5(1:2.5)	10	100	250	20
RB6(1:3)	10	100	300	20
RB7(1:4)	10	100	400	20
RB8(1:5)	10	100	500	20
RB9(1:6)	10	100	600	20
RB10(1:7)	10	100	700	20

Evaluation of Bioflexy Film

Thickness of Formulated Bio-flexy Films

Thickness of Formulations was measured using Digital micrometer.

Surface pH of Formulated Bio-flexy Films

Surface pH of formulated films was determined by using digital pH meter. It should be neutral or close to soft palatal pH otherwise formulation might cause irritation to soft palatal mucosa. The formulated bio-flexy films were kept in contact with 1 mL of distilled water at room temperature for 1 hour. The pH was measured in triplicate. Compatibility of formulations with soft palatal pH is essential.

Folding Endurance of Formulated Bio-flexy Films

Calculated manually by repeated folding 1 film at same place until it broke or up to 300 times.

Weight Variation of Formulated Bio-flex Films

Weight uniformity of formulated films was determined by weighing 10 formulations of 1 cm^2 diameter and determined average weight.

Percentage Moisture Uptake of Formulated Bio-flexy Films

PMU was determined so as to check the physical stability of the prepared bio-flexy films in high moist conditions. Bio-flexy films of 1cm diameter were kept in saturated solution of aluminium chloride in desiccator. The humidity inside the desiccator was maintained at 79.5%. Removed the films after 3 days, weighed and calculated percentage moisture absorption.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(3), 1105-1113 | ISSN:2251-6727

$$Percentage\ moisture\ uptake = \frac{(Final\ weight\ of\ films - Initial\ weight\ of\ films)}{Initial\ weight\ of\ films} \times 100$$

In-Vitro Release Study of Formulated Bio-flexy Films by Modified M.S. Diffusion

The In vitro drug diffusion was carried out in M.S diffusion apparatus. This was static method and employed complete replacement of the sample. 2 cm square of Risperidone loaded Bio-Flexy films was kept in the donor compartment and the receiver compartment was filled with 13 ml of buffer. The complete sample was withdrawn after 30 mins. And the receiver compartment was refilled with 13 ml of fresh buffer. The samples were withdrawn at regular time intervals for 8 hours. The amount of drug release was assessed by measuring the absorbance at 325 nm using U.V spectrophotometer.

RESULTS AND DISCUSSION

Isolation of biomaterial

The biopolymers from Guava and Banana were isolated from natural edible sources by simplified economic process. The biopolymer was isolated and calculated its percentage yield**(table 3).**Isolated biopolymer quantity was used during the formulations of bioflexi film.

Biopolymer	% Yield
Psidium guajava	60.5%
Musa acuminata	63.7%

Table 3: Percentage yield of biopolymers

Physicochemical Characterization of Isolated Biopolymers

Biopolymers were identified by subjected to various physicochemical parameters such as Color, Odor, Texture and Melting point. Chemical tests for determination of presence of carbohydrates, proteins and starch. They showed positive results with Molisch test and Biuret Test which clearly demonstrated a presence of carbohydrates and proteins**(table 4).**

Table 4: Physicochemical Characterization Tests of Bioploymers

Biopolymer	Colour	Odour	Melting Point	Carbohydrate	Protein	Reducing sugar	Starch
Psidium guajava	light brown	characteristics	210°C	Purple Colour (Positive)	Violet Colour (Positive)	Brick Red Precipitate (Positive)	Absent
Musa acuminata	off white creamish	characteristics	198°C	Purple Colour (Positive)	Violet Colour (Positive)	Brick Red Precipitate (Positive)	Absent

Drug -Polymer Interaction Study

The drug polymer interaction showed no significant difference with that of pure risperidone therefore drug-excipient interaction did not occur (**Table 5 and 6**).

Table 5 -Interaction studies of drug and biopolymer from Psidium guajava

Ratio (Risperidone:Polymer)	Wet method (nm)	Dry method (nm)
1:1	310	318
1:3	305	311
3:1	316	318

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(3), 1105-1113 | ISSN:2251-6727

Table 6 -Interaction studies of drug and biopolymer from Musa acuminata

Ratio (Risperidone:Polymer)	Wet method (nm)	Dry method (nm)
1:1	313	317
1:3	307	314
3:1	315	310

UV Scanning of Resperidone

The calibration curve was prepared by recommended procedure as shown in figure 2. Linear relationships between absorbance and concentration held over and other parameters are given in table 7.

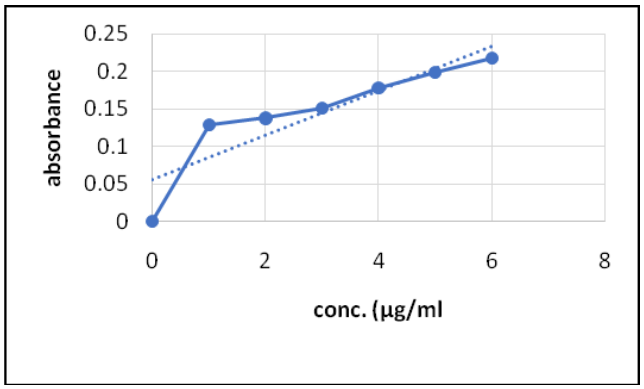

Figure 2: Calibration vurve of Risperidone

Table 7: Parameters from calibaration curve of Risperidone

Parameters	Risperidone
λ_{max}, nm	415
Beer's limit (µg/ml) 10-55	05-40
Molar absorptivity ($lmol^{-1}cm^{-1}$)	$7.3932x10^4$
Sandel sensitivity (µg cm^{-2}/0.001A)	0.005521
Correlation coefficient	-0.99247
Regression equation	
Slope (b)	-0.01038
Intercept (a)	1.11565
Standard deviation	0.0186

% Yield of Nanosized Risperidone

The % yield of nanosized risperidone was found to be 97.77%.

EVALUATION PARAMETERS OF BIO-FLEXY FILMS

Thickness of Formulated Bio-flexy Films

As polymer concentration was increased, thickness of films increased proportionally.

The thickness of nanosized Risperidone loaded Bio-Flexy films containing**psidiumguajava (RG1-RG10)** was found to be in range of 0.32 +-0.03mm to 0.41+-0.06mm.

The thickness of nanosized Risperidone loaded Bio-Flexy films containing **Musa acuminata** (**RB1-RB10**) was found to be in range of 0.27+-0.05 mm to 0.35+-0.04 mm.

Surface pH of Formulated Bio-flexy Films

The Surface pH of nanosized Risperidone loaded Bio-Flexy films containing **psidium guajava** biopolymer **(RG1-RG10)** was found to be in range of 7.02 +-0.02 to 7.04+-0.004.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(3), 1105-1113 | ISSN:2251-6727

The Surface pH of nanosized Risperidone loaded Bio-Flexy films containing Musa **acuminata** (**RB1-RB10**) was found to be in range of 7.20+-0.04 to 7.21+-0.02.

Folding Endurance of Formulated Bio-flexy Films

Folding Endurance of all the formulation was measured and it showed that flexibility was proportionately increased significantly as concentration of polymer in formulation was increased. The Bio-flexy films were devoid of brittleness showing significant folding endurance due to presence of dextrose and fructose as excipients in optimized ratio. The Folding Endurance of 1 sq. cm Films were found to be in range of 74-187 for nanosized Risperidone loaded Bio-flexy films.

The Folding Endurance of nanosized Risperidone loaded Bio-Flexy films containing**psidium guajava(RG1-RG10)** biopolymer was found to be in range of 89-134.

The Folding Endurance of nanosized Risperidone loaded Bio-Flexy films containing **Musa acuminata** (**RB1-RB10**) biopolymer was found to be in range of 94-187.

Weight Variation of Formulated Bio-flex Films

The Weight Variation of all the Formulation was proportionally increased as polymer concentration was increase. The weights of 1 Sq.cm Films were found to be in range of 19.52 to 48.40 mg for nanosized Risperidone loaded Bio Flexy films.

The Weight Uniformity of nanosized Risperidone loaded Bio-Flexy films containing**psidiumguajava (RG1-RG10)** biopolymer was obtained between 23.71+0.2mg to 38.21+-0.30.

The Weight Uniformity of nanosized Risperidone loaded Bio-Flexy films containing Musa **acuminata** (**RB1-RB10**) biopolymer was obtained between 19.31+0.11 mg to 34.41+-0.2mg

In-Vitro Release Study of Formulated Bio-flexy Films by Modified M.S. Diffusion

In-Vitro Release Study of Formulated Bio-flexy Films was performed by Modified M.S. Diffusion Apparatus for up to 48 hours. The release order of drug in formulations RG**1-RG10** comprised by **psidium guajava** depends on T50% and T80% was like this RG**6(1:6) > RG9(1:9) > RG4(1:4) > RG10(1:10)> RG8(1:8) >RG5(1:5)> RG3(1:3)> RG1(1:1)> RG2(1:2) > RG5(1:7) (Fig 3).**According to an evaluation parameter, RBV6 (Risperidone: beta vulgaris (1:6) Bio-flexy film was selected as the best formulation as it showed significant values of **T50%: 6 hours, T80: 28** hours and having square-0.9892, Peppas Korsemeyer as best relevant model, exhibit Fickian release Diffusion (Higuchi Matrix) mechanism in comparison to other formulations of same biopolymer.

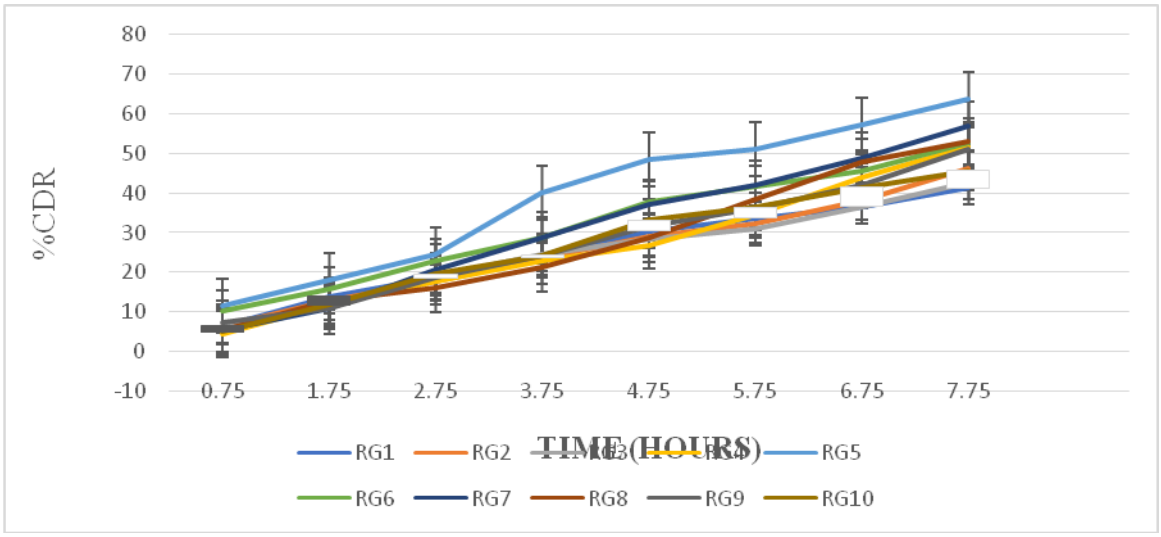

Figure 3: In Vitro drug release from bioflexy films of Psidium guajava

The release order of drug in formulations **RB1-RB10** comprised by Musa **acuminata** depends on T50% and T80% was like this **RB4(1:4) > RB8(1:8) > RB5(1:5) > RB7(1:7)> RB9(1:9) > RB6(1:6) >RB3(1:3)**

Journal of Chemical Health Risks
www.jchr.org
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>RB1(1:1)>RB10(1:10) >RB2(1:2) (fig 4). According to an evaluation parameter, RB5(Risperidone: Musa acuminata (1:5) Bio-flexy film was selected as the best formulation as it showed significant values of **T50%: 4 hours, T80: 29 hours** and having R square-0.9300, Peppas Korsemeyer as best relevant model, exihibitFickian release Diffusion (Higuchi Matrix) release in comparison to other formulations of same biopolymer.

RG5 and RB5 were selected as best formulation on the basis of drug release.

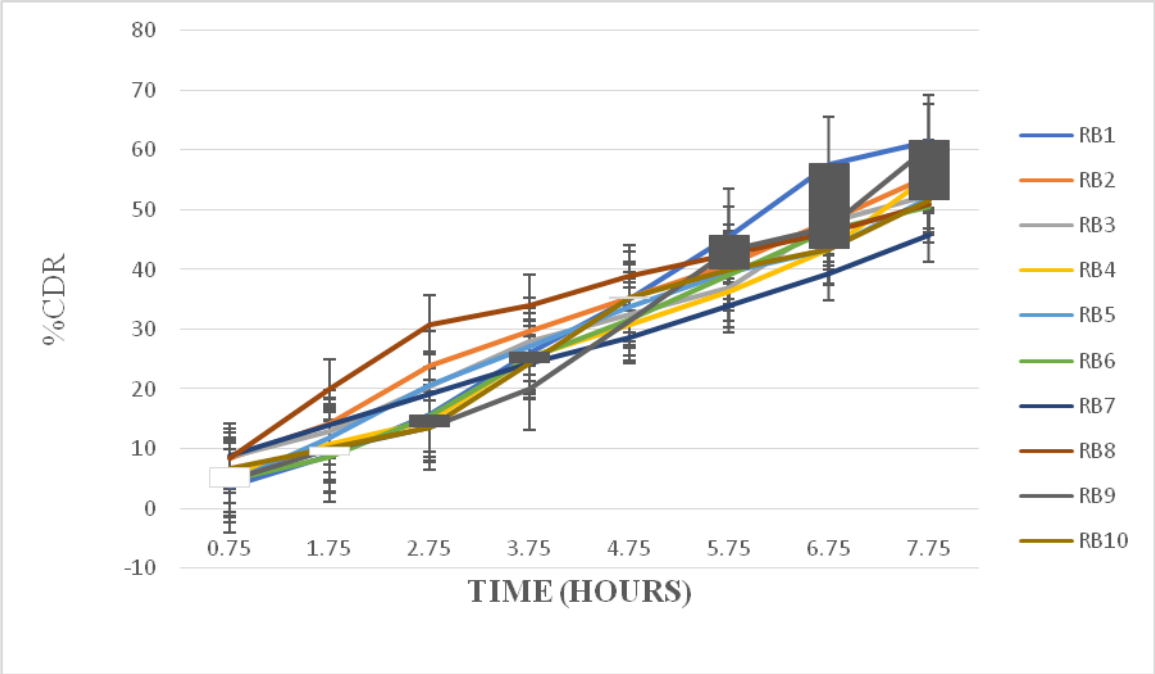

Figure 4: In Vitro drug release from bioflexy films of Musa acuminata

Conclusion

In this research work, enhance a possibility of nanosized Risperidone loaded bioflexi film for a delivery of A.P.I via soft palatal route to particular region of brain is explored.The conclusion was drawn that antipsychotic molecules like Risperidone can be effectively delivered to brain via soft palatal Route by formulating Bio-flexy Films containing nanosized drugs molecules for the management of psychosis. Biopolymers are incorporated as bio-excipients and adhesive film formers that provided controlled release for prolonged period of time. This approach offers low dosing level up to 25-100 folds which in turn causes minimization or devoid of adverse reactions offered by the Risperidone (like Suicidal tendency,weight gain, tardive dyskinesia) upon oral administration. This approach can also provide complete patient compliance, economic, safer to patients with lesser API burden in the body.

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