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A Smart Approach for Delivering of Risperidone using Vigna radiata to Prepare Bioflexi film for Oro Trans Soft Palatal Delivery

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KEYWORDS
Risperidone, Bioflexy, Vigna radiata, Bioploymer, Franz's Diffusion cell.

ABSTRACT:

Objective: The purpose of the present study was to formulate and evaluate nanosized risperidone loaded mucoadhesive bioflexi films for effective treatment of atypical antipsychotic. For the preparation of bioflexi films, biopolymer was isolated from seeds of *Vigna radiata (Moong Daal)*. After the extraction of biopolymer, it was subjected for various evaluation parameters.

Methods: A novel method is used for the nanosizing of risperidone and after that bioflexyfilms were prepared by using different ratio of drug and biopolymerusing dextrose as flexicizer and tween 80 as permeation enhancer. After the preparation of different formulations every formulation was studied for different evaluation parameters to find out the best drug polymer ratio.

Results: The formulations were characterized including uniformity of weight, drug content, folding endurance, and thickness. To study the stability of the formulations and *in vitro* dissolution of the experimental formulations were performed to determine the amount of risperidone present in the film and scanning electron microscopy of the prepared bioflexi films was taken to see the drug distribution pattern. Drug-excipient interaction studies were carried out using UV spectroscopic technique by using wet method and dry method. *In vitro* dissolution studies showed that the drug distribution in the bioflexi film was homogeneous and it was found that the maximum drug release in 24 h with RVR 6. *In vitro* skin permeation study was also conducted in a modified Franz's diffusion cell which shows that the maximum permeation with the formulation RVR 6

Conclusion: The bioflexifilms were found to be suitable for formulating as per the characterization and there was no interaction found between the drug and polymer.

Introduction

The soft palatal 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] Despite a global popularity of oral drug delivery route, trans soft palatal route are attractive, impressive and outstanding advantageous due to their non-mobile, non-invasive, and show highly mucoretentionproperty.It has high bio-availability, therefore, lower doses of a medicament and show fewer side effects. In addition, the soft palatal drug delivery system, avoid the first-pass metabolism by the liver and metabolism by G.I tract will decrease the possible side effects correlate with the risperidone metabolite. [2]

A soft palatal region of oral mucosa maintains inherent properties, which does not restrict when a patient or victim does a uniform movement and activities like eating, talking and drinking, etc. A soft palatal drug

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delivery zone is more adjustable and moveable epithelial muscle can be simply retrieved for insertion of dosage form. When the dosage form is inserted at the soft palatal region with bioadhesive and mucoadhesive characteristics, a dosage form will stay constant at the administered site for a prolonged period of time in order to reach a controlled release of a drug. Soft palatal route is one of the most effective route for drug administration and offer all the benefits recommended by the other route such as buccal and sublingual drug delivery however this path of drug delivery is useful for the collective effects of the direct absorption of drug from soft palatal site and the reduction in rate of excretion of drug permit for an improved bioavailability of the medicaments with a lesser dosage and low frequent administration via the absorption site of soft palatal. Also, this delivery route, decrease the toxicity and reduce the excess of costly drug because of decrease in the primary amount of drug filling concentration, prevent the erosion of the medicaments in the biological fluids, and permit targeting and positioning of a drug at a particular site of the brain. In our body several transmucosal locations are available, but soft palatal mucosa was also found to be the most suitable, beneficial and simple acceptable innovative site for a delivery of medicaments via systemic circulation as Retaining dosage forms, it has showed sufficient vascular region and quick cellular retrieval time, soft palatal has a flat surface and it proceeds a noble flexibility which is essential to avoid the irritation and discomforts. Soft palate drug delivers a constant delivery of medicaments for a prolonged time. [3,4]

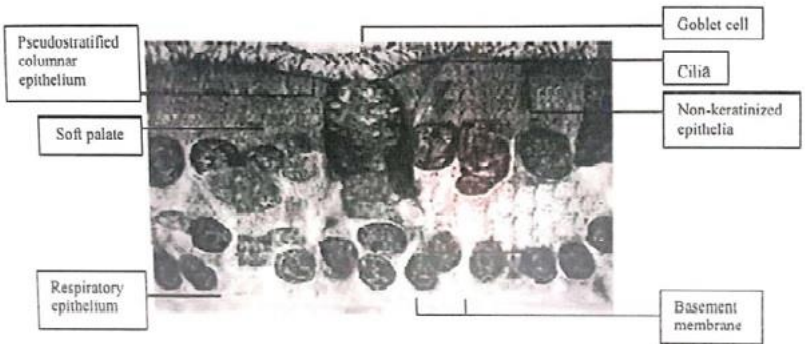

Figure 1: Soft Palatal Region

This drug delivery system provides ease administration of a drug. This route of drug delivery also Avoids first pass metabolism. Decrease in dose intake can be determined, and also reduce the side effects of the drug. 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.For those drugs which are unstable in acidic pH, then this route is very effective for those medicinesoft palatal route is an effective route for those drugs which show poor bio availability from oral route. In this drug delivery system, drug molecules follow passive diffusion, from the soft palatal region. Drugs which show a short half-life can be given by this method approximately (2-8 hours) e.g.: nitroglycerine (2 hours) and isosorbide mononitrate (2-5 hours). Due to the presence of a thin mucin film exist on the surface of oral cavity. Provides a significant opportunity to retain drug delivery system in contact with soft palate region for prolonged period of time with the help of mucoadhesive presence.

The soft palate route is one of the most suitable sites for transdermal bio flexi films to be placed for targeted drug delivery to distinctive parts like brain.

MATERIALS AND METHODS

Drug: Risperidone was obtained as a gift sample from Gentech Healthcare, Delhi. The natural biopolymer was extracted from the seeds of Vigna radiata (moong daal) and the natural source was procured from the market.

Isolation of biopolymer from the Fruits

1 kg of moong daal was procured from the market, and converted into the paste by the help of grinder. Then

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add 400ml of distilled water 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 3000 rpm for 15 minutes. After centrifugation, the supernatant layer was taken and treated with chloroform (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. Stored in a well closed container for further use.

Physicochemical Characterization of Biopolymers-

The various physiochemical characterization of isolated biopolymer was performed like color, odor, solubility, melting point and various chemical tests were performed.

(a) Texture, Colour and Odour of the biopolymer were observed manually through physical examination.

(b) Melting point: determined by capillary method by using melting point apparatus. The bio-polymer was filled inside a capillary tube and inserted in melting point apparatus and the temperature was determined by means of thermometer.

(c) Solubility: determined in different solvents (chloroform, methanol, distilled water, acetone, carbon tetrachloride).

(d) **Test for carbohydrates**

a. **Molisch Reagent Test:** this test was used to identify a carbohydrate presence in Biopolymer. 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.

(e) 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.

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

(g) 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 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 λmax, 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, λ 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

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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 Bioflexi Film by solvent casting method

10 mg of Nanosized risperidone was triturated with biopolymer obtained from vigna radiata in different ratio (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).**

Formula	Drug (Risperidone) (mg)	Dextrose (mg)	Polymer: Vigna radiata (mg)	Water (ml)
RVR1(1:0.5)	10	100	50	20
RVR2(1:1)	10	100	100	20
RVR3(1:1.5)	10	100	150	20
RVR4(1:2)	10	100	200	20
RVR5(1:2.5)	10	100	250	20
RVR6(1:3)	10	100	300	20
RVR7(1:4)	10	100	400	20
RVR8(1:5)	10	100	500	20
RVR9(1:6)	10	100	600	20
RVR10(1:7)	10	100	700	20

Table 1: Formulation of Bioflexy film

Evaluation of Bioflexi Film

Thickness of Formulated Bio-flexi Films

Thickness of Formulations was measured using Digital micrometer.

Surface pH of Formulated Bio-flexi 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-flexi Films

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

Weight Variation of Formulated Bio-flexi 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-flexi 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.

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

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

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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-Flexi 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.

Figure 2: Modified MS Diffusion cell

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 2).**Isolated biopolymer quantity was used during the formulations of bioflexi film.

Formulation	% Yield
RVR1(1:0.5)	60.02
RVR2(1:1)	60.10
RVR3(1:1.5)	60.08
RVR4(1:2)	61.02
RVR5(1:2.5)	60.03
RVR6(1:3)	60.08
RVR7(1:4)	61.05
RVR8(1:5)	61.04
RVR9(1:6)	60.09
RVR10(1:7)	60.78

Table 2: 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 3).**

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Biopolymer	Colour	Odour	Melting Point	Carbohydrate	Protein	Reducing sugar	Starch
Vigna radiata	light white	odourless	207°C	Purple Colour (Positive)	Violet Colour (Positive)	Brick Red Precipitate (Positive)	Present

Table 3: Physicochemical Characterization Tests of Bioploymers

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 4**)

Ratio (Risperidone:Polymer)	Wet method (nm)	Dry method (nm)
1:1	315	314
1:3	318	308
3:1	313	317

Table 4 -Interaction studies of drug and biopolymer from vigna radiata

UV Scanning of Resperidone

The calibration curve was prepared by recommended procedure as shown in figure 3. Linear relationships between absorbance and concentration held over and other parameters are given in table 5.

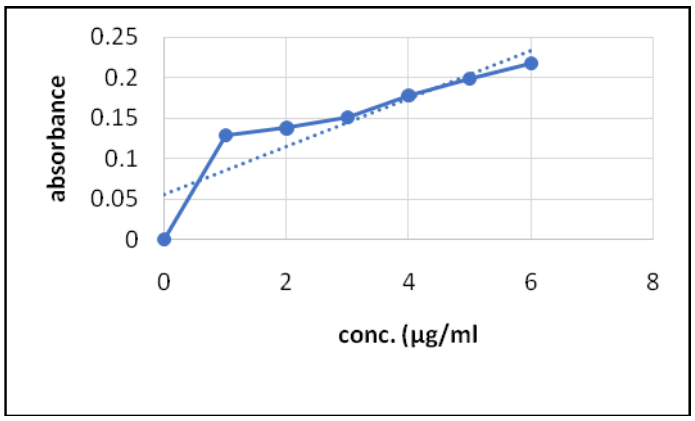

Figure 3: Calibration curve of Risperidone

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

Table 5: Parameters from calibaration curve of Risperidone

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% Yield of Nanosized Risperidone

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

EVALUATION PARAMETERS OF BIO-FLEXI FILMS

Thickness of Formulated Bio-flexi Films

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

The thickness of nanosized Risperidone loaded Bio-Flexi films containing**vigna radiata** was found to be in range of 0.33+- 0.05 mm to 0.40+0.02mm.

Formulation	Thickness in mm
RVR1(1:0.5)	.34
RVR2(1:1)	.33
RVR3(1:1.5)	.31
RVR4(1:2)	.31
RVR5(1:2.5)	.40
RVR6(1:3)	.38
RVR7(1:4)	.32
RVR8(1:5)	.38
RVR9(1:6)	.39
RVR10(1:7)	.34

Table 6: Thickness of Formulated Bio-flexy Films

Surface pH of Formulated Bio-flexi Films

Prepared formulations suitable for soft palatal delivery platform as they are in the range of physiological pH. The Surface pH of nanosized Risperidone loaded Bio-Flexy films containing **Vigna Radiata(RVR1-RVR10**) biopolymer was found to be in range of 7.01+-0.03 to 7.06+-0.03.

Formulation	Surface pH
RVR1(1:0.5)	7.01
RVR2(1:1)	7.00
RVR3(1:1.5)	7.06
RVR4(1:2)	7.05
RVR5(1:2.5)	7.03
RVR6(1:3)	7.06
RVR7(1:4)	7.05
RVR8(1:5)	7.03
RVR9(1:6)	7.01
RVR10(1:7)	7.01

Table 7: Surface pH of bioflexi films

Folding Endurance of Formulated Bio-flexi 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.

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The Folding Endurance of nanosized Risperidone loaded Bio-Flexy films containing Vigna **Radiata(RVR1-RVR10**) biopolymer was found to be in range of 88-167.

Formulation	Folding endurance
RVR1(1:0.5)	88
RVR2(1:1)	92
RVR3(1:1.5)	98
RVR4(1:2)	120
RVR5(1:2.5)	143
RVR6(1:3)	156
RVR7(1:4)	162
RVR8(1:5)	165
RVR9(1:6)	167
RVR10(1:7)	166

Table 8: Folding Endurance of nanosized Risperidone loaded Bio-Flexy films

Weight Variation of Formulated Bio-flexi 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 Flexi films.

The Weight Uniformity of nanosized Risperidone loaded Bio-Flexy films containing **Vigna Radiata(RVR1-RVR10**) biopolymer was obtained between 22.50+-0.20 mg to 48.40+-
0.30 mg

In-Vitro Release Study of Formulated Bio-flexi 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 **RVR1-RVR10** comprised by **Vigna radiata** depends on T50% and T80% was like this **RVR6(1:6) > RVR5(1:5) > RVR2(1:2) > RVR7(1:7)> RVR9(1:9) > RVR1(1:1) >RVR3(1:3) >RVR4(1:4)>RVR(1:8) >RVR10(1:10).**According to an evaluation parameters, RVR6 (Risperidone: vigna radiata (1:6) Bio-flexy film was selected as the Best formulation as it showed significant values of **T50%: 2 hours, T80: 29 hours** and having R square-0.9219, Peppas Korsemeyer as best relevant model, exhibit Diffusion (Higuchi Matrix) release mechanism in comparison to other formulations of same biopolymer.

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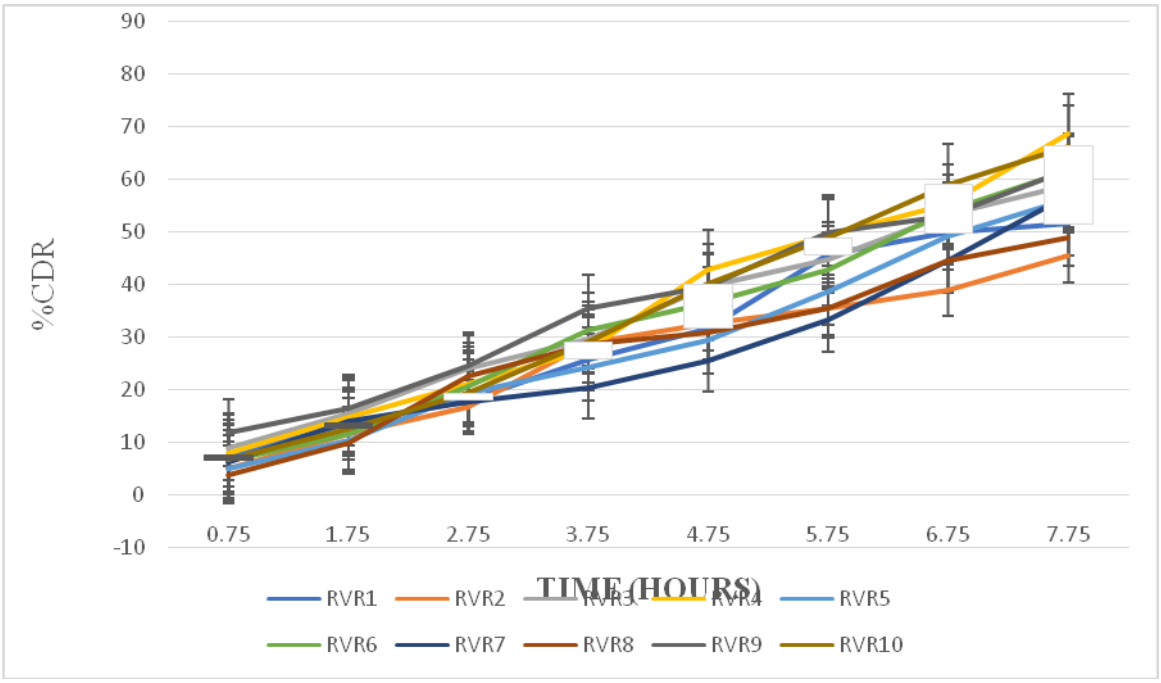

Figure 4: In Vitro drug release from bioflexifilms

RVR 6 was selected as best formulation on the basis of drug release.

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. This novelistic work was scientifically proven by suitably nanosizing active pharmaceutical ingredient formulating in bio flexy dosage forms and determined its pharmacological action, significant antipsychosis action was produced. The result are correlated with the in-vivo release which prove that minimum amount of drug reaches to the brain via a neural pathway and retained for prolonged period of time.

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. Thebiopolymer was devoid of irritancy to soft palate because of its inertness, so this biopolymerwas selected for formulating risperidone flexi-film. Flexi film was prepared by solvent casting technique which is the easiest and reproducible method to prepare flexi film without need of any sophisticated instruments. Drug to Polymer ratio was chosen at ten levels. RVR 6 was found as best formulation.

References

1. URL:http://en.wikipedia.org/wiki/blood supply to soft palate.html, Accessed on date: (08 Apr 2013).
2. M.J. Rathbone, J. Hadgraft, Absorption of drugs from the human oral cavity, Int. J.Pharm. 74,9-24,(1991).
3. M.E. de Vries, H.E. Bode, J.C. Verhoef, H.E. Junginger , Development in buccal drug delivery, crit. Rev.Ther.Drug Carrier Syst. 8,271-303 (1991)
4. H.E. Bode, M.E. De Vries, H.E. Junginger, Mucoadhesive polymers for the buccal delivery For Structural - adhesiveness relationships J.control Release 13, 225-231,(1990).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(3), 1095-1104 | ISSN:2251-6727

5. R.B. Gandhi. J.R. Robinson, Oral Cavity as a site for bioadhesive drug delivery, Adv.Drug Deliv. Rev. 13, 43-74,(1994).
6. C.A. Squier , N.W. Johnson, R.M. Hopps, The Organization of Oral Mucosa, Human Oral Mucosa, Development, Structure and Function, Blackwell Scientific Publication, Oxford, pp-7-15, (1976).
7. C.A. Squler, N.V. Johnson, Permeability of Oral Mucosa, Br. Mcd. Bull. 31: 1969-1975,(1975).
8. Behl CR, Pimplaskar HK, Sileno AP, de Meireles J. Romeo VD. Effects of Physicochemical properties and other factors on systemic brain drug delivery.Adv. Drug Deli. Rev.: 29: 89-116.(1998).
9. Chein YW, Novel drug delivery systems. 2nd ed. New York: Marcel Dekker, Inc.; p. 229, (1992).
10. Ranade, V., (1991), Drug Delivery Systems: Transdermal Drug Delivery." Clinical Pharmacol. 31(6), pp. 401-408.
11. Costa, P., Ferreira, D. C., Morgado, R., and Sousa, Lobo, J. M., (1997). "Design and Evaluation of a Lorazepam Transdermal Delivery System." Drug Dev. Ind. Pharm..23,pp. 939-944.
12. Madhav. N V S., Yadav, P. A., (2011) "Lip: An impressiveand idealistic platform for drug delivery." J Pharm Res., 4(4). pp. 1060-1062
13. Skandalakis, J. E. Skandalakis, P. N., Skandalakis, L. J.. Surgical Anatomy and Technique: A Pocket Manual". New York: Springer-Verlag: 1995.
14. Pensler, J. M., Ward, J. W., Parry, S. W.. (1985) "The superficial musculoaponeurotic system in the upper lip: an anatomic study in cadavers". PlastReconstr Surg. 75(4), pp. 488-94.
15. Madhav, S N V., et al., (2017) Review on Biopolymers as Novel Bio-Excipients in Drug Delivery System" European Journal of Pharmaceutical and Medical Research, 4(6), pp.247-250.
16. Madhav, S N V., et al., (2018) "Isolation and characterization of novel Mucoadhesive Biomaterial from Phoenix dactylifera". International Current Pharmaceutical Journal, 1 (8), pp. 205-208.
17. Madhav. S. N. V., et al.,(2011) "A Novel. Potent, Bio-Emulsifier from the fruit pulp of Manilkara zapota for formulating Escitalopram Microemulsions", International Journal of Pharmaceutical Technology Research. 3 (2), pp. 929-933.
18. Madhav S. N. V. et al. (2011) "Formulation & Evaluation of Nimesulide Bio-Micro Dwarfs using A Novel Bio-retardant from the Rhizomes of Zingiber officinale",International Journal of Pharmaceutical Technology Research. 3(1), pp. 221-224.
19. Kandimalla, K. K, et al., (2013) Traffic jam at the Blood-Brain Barrier promotes greater accumulation of Alzheimer's disease Amyloid-ß Proteins in the Cerebral Vasculature". Molecular Pharmaceutics Journal, 10(5), pp. 1557-1565.
20. Madhav. S. N V. et al., "A smart soft palatal platform for oral Transmucosal delivery by using drug-loaded Mangifera indica bio-plate." Proceedings of Indian Pharmaceutical congress held at BHU on 23-25 December 2007.
21. Kalviainen. R. (2001) "Long-Term Safety of Tiagabine". Epilepsia Journal. 42 (3), pp.45-48.
22. Madhav, S. N. V.. et al. (2016) "Development and Evaluation of Carbamazepine loaded Bio-Flexy layers For Brain Targeting through Soft Palate". Proceedings of International Conference on Energy. Functional Materials & Nanotechnology (ICEFN 2016), organized by Nanoscience and Nanotechnology centre. Department of Chemistry,27-29th March 2016 in Kumaun University, Nainital.