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Development Process for Nanosized Aripiprazole Loaded Films Using a Biopolymer from *Zea mays* and Its Performance Evaluation

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ABSTRACT

Aim of the current study was to develop nanosized aripiprazole loaded bio-flexy films using biopolymer from *Zea mays* for oro-translabial drug delivery. Nanosizing reduces the particle size into nano level thereby reduces the dose and also the dose related serious side effects of aripiprazole. Aripiprazole was nanosized by novel method using 1,2,3-Propanetriol as Nanosizant. Ten nanosized Aripiprazole loaded films viz. FZ1-FZ5 and FM1-FM5were prepared by Solvent Casting Technique using different ratios (1:1, 1:2, 1:3, 1:4 and 1:5) of biopolymer from *Zea mays* and HPMC as film former, 1,2,3-Propanetriol and D-glucose as flexicizer. The isolated biopolymer was off-white in colour, biodegradable and biocompatible in nature. All formulations were thin, smooth, transparent to translucent in appearance and flexible in nature. The amount of film former influenced the release properties of formulations. Formulation FZ3(1:3) was best optimized formulation performance with 148 times mucoadhesion time, 99.30% drug content uniformity, and released drug over a period of 36 hrs. Nanosized aripiprazole loaded films were developed and optimized for delivery via oro-transmucosal route and can be effectively applied on labial mucosa for effective treatment and management of schizophrenia, depression, bipolar disorder and irritability associated with autism.

1. INTRODUCTION

Depression is a debilitating multifacetic disorder, which has dramatic impact on normal human behavior (1). According to Eugen Bleuler depression is a part of core symptoms of schizophrenia. Although depression can occur at any stage of schizophrenia but it is most common during acute phase than stable patients (2). According to World Health Organization, major depression is ranked as the leading cause of disability in middle and high-income countries. At international platform, 4.1% of the total global burden of disease is due to major depression. If current trends continue, it will become the leading cause of disease burden by the year 2030 (1). Aripiprazole has been approved by Food and Drug Administration in 2002 for the treatment of schizophrenia (3) and most prescribed new medication worldwide for schizophrenic illness (4).

Aripiprazole is also effective in the treatment and management of acute mania, mixed episodes associated with bipolar disorders, and also as an adjunct treatment of depression. Aripiprazole is second generation atypical antipsychotic drug and belongs to benzisoxazole derivative class. It has partial agonistic activity at serotonin 5-HT1A-receptor and dopamine D2 receptors as well as antagonistic properties at 5-HT2A-receptor. It is available in tablet, orally disintegrating tablets, and solution and intra muscular injection (5).

Although aripiprazole is very useful in different neurological disorders it has many adverse effects such as weight gain, hyperlipidemia, hyperprolactinemia, hypotension, somnolence, and sedation (6). U.S.F.D.A. issues a Black Box Warning for Aripiprazole Drug moiety, and it is the strongest warning issued by U.S.F.D.A. about any serious potentially fatal, life-threatening or permanently disabling adverse effects of specified drugs. It clearly indicates that there are enough proofs for drug that it causes significantly serious or life-threatening adverse effects without definite cause effect correlation (7).

Labium inferioris extends from the superior free vermilion edge, to the commissures laterally, and to the mandible inferiorly. Labium inferioris is lined externally by skin and internally by mucous membrane. The mucous membrane of lip is highly vascularized, with enormous blood capillaries giving it reddish color. The labium inferioris is supplied from the inferior labial branches of facial artery, one of the six non-terminal branches of the external carotid artery. The mucous of lip is non-keratinized in nature and composed of stratified squamous epithelium. All muscles acting on the lips are supplied (motor supply) by the nerve of the second pharyngeal arch, the facial nerve (7th cranial nerve) (8-9). The labium inferioris

receives nerve supply from the mental nerve innervated by mandibular branch of the facial nerve (via the inferior alveolar nerve) (10).

Although tremendous advancements in the field of drug delivery are done but the oral route is considered as most preferred delivery route in regards to patient acceptability, ease of administration and economical. The mucoadhesive polymers plays a significant role in achieving higher dosage form retention time through formation of various mucoadhesive bonds. These polymers are possessed of carboxyl and sulfate functional groups. The possible solid dosage forms for mucoadhesive drug delivery are tablets, lozenges, patches, films, wafers and micro or nanoparticulates (11). Recently mucoadhesive buccal strips are incorporated in European Pharmacopoeia 7.4 which makes these dosage form a promising alternative to conventional dosage forms (12).

Corn is obtained from kernels of *Zea mays*, is 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 sources of tocopherols, especially γ-tocopherol. Corn starch is well recognized for its uses in food industry and in pharmaceutical industries as diluent. Roasted corn kernels are used as coffee substitute (13-14).

In the current research work nanosized aripiprazole loaded films using a biopolymer from *Zea mays* were developed for oro-translabial mucosal drug delivery platform.

2. MATERIALS AND METHODS

Aripiprazole was received as gift sample from Sun Pharma (Mumbai), India. *Zea mays* was procured from local market of Dehradun, Uttarakhand, India. HPMC, D-glucose, maltodextrin and all other chemicals and solvents were of analytical reagent grade.

2.1: 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 4000rpm for 1hr. Then it was centrifuged at 3000 rpm to remove the extraneous matter. The supernatant liquid was treated with optimized quantity of propanone and kept in refrigerator for 24hrs. The isolated bio-material was separated by centrifugation at

4000rpm for 25 mins. The bio-material was dried in desiccator for 48 hrs. The bio-material extraction was repeated 6 times & practical yield was reported. (15)

2.2: Physicochemical characterization and spectral analysis of the isolated bio-material

The isolated bio-material was tested for various physicochemical properties like colour, odour, solubility, color changing point, chemical tests for carbohydrates (molisch's test, benedict's test), proteins (biuret test) and starch, SEM analysis and spectral studies like IR and NMR Spectra was performed using Shimadzu IR Tracer-100 (16).

2.3: Drug excipients interaction study

The drug interaction study was performed wet and dry method. The drug was physically mixed with excipients in dry method and in wet method the physical mixture was treated with 2ml of distilled water in the ratios of 1:1, 1:3 and 3:1 and kept for a period of 3 days. Both the mixtures were dissolved in methanol and then analyzed by TLC and UV Spectrophotometric method at 221nm (17-18).

2.4: A Novel High through Put Screening Method for determining the nanoparticle size range by characterization by U.V. spectroscopic method

If drug particles were dissolved in nano level it shows increase in % transmittance with decrease in absorbance. The increase in %T which confirms that much % of particle are falling above 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 (19).

2.5: *Ex-vivo* Permeability Study

Drug solution of 1mg/ml was prepared and 1ml drug solution added in 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.

2.6: Formulation of nanosized aripiprazole loaded flexy films

Aripiprazole was nanosized using novel method. The drug was dissolved in suitable solvent and 10 µl of 1,2,3-Propanetriol was added as nanosizant in it (20). 10 ml of distilled water was added into it and sonicated for 5 cycles (each cycle of 3 mins). The solution was micro

centrifuged at 10,000rpm for 15 mins and residue was dried and collected. Nanosized Aripiprazole loaded flexy films using biopolymer and standard polymer i.e. HPMC were prepared by using "Solvent casting method". In this method biopolymer from *Zea mays* and HPMC was accurately weighed in different ratios and triturated with 10µl of 1,2,3-Propanetriol, and 80mg of D-glucose as flexicizer. 10ml of distilled water added into it and subjected for mechanical stirring for 30mins shown in Table 1. 10mg of drug was dissolved separately in ethanol. The nanosized drug solution was added to the polymeric solution under stirring 4,500 rpm. The polymeric solution was poured on petridish for natural drying of about 24 hrs.

Table No. 1: Formulation table of Aripiprazole loaded flexy films of *Zea mays* and HPMC

Formulation	FZ1 (1:1)	FZ2 (1:2)	FZ3 (1:3)	FZ4 (1:4)	FZ5 (1:5)	FM1 (1:1)	FM2 (1:2)	FM3 (1:3)	FM4 (1:4)	FM5 (1:5)
Aripiprazole (mg)	10	10	10	10	10	10	10	10	10	10
Zea mays (mg)	1%	2%	3%	4%	5%	-	-	-	-	-
HPMC (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

2.7: Evaluation of nanosized Aripiprazole loaded flexy films

2.7.1: 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 ($1cm^2$) was transferred into a 100ml volumetric flask containing 7ml of phosphate buffer of pH 7.4 and 1ml of methanol. The contents of flask were stirred for 4 hrs on magnetic stirrer. The drug content was then determined after appropriate dilutions by using an UV spectrophotometer (Shimadzu 1800) (18).

The drug content was calculated by using below equation:

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

2.7.2: Folding endurance and surface pH

The selected films were subjected repeatedly folding the strip (of area 2cm^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 (18).

2.7.3: Mucoadhesion study

The mucoadhesive property of prepared films was evaluated by rotating cylinder 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 were adhered to the membrane with gentle pressing. Then the cylinders were rotated at 100rpm in 900ml of phosphate buffer pH 7.4 at 37±˚C. After each 30 min and up to 48hrs the strip was observed for any dislodgement or disintegration from the mucosal surface. The results were compared with the standard films of HPMC (18).

2.7.4: *In-vitro* drug release study

The *in-vitro* drug release study was carried out by using the dynamic franz diffusion cell method. Egg shell membrane was tied on the donor compartment and flexy strip of 1 cm^2 area was kept on above the membrane and the receiver compartment were filled with 7ml of phosphate buffer pH7.4. 4ml of sample was withdrawn at the intervals of 0, 10, 20, 30, 60, 120, 180, 300, 360, 480 and1440mins and replaced with 4ml of fresh medium. The amount of drug released was assessed by measuring the absorbance at 221nm using UV spectrophotometer (Shimadzu 1800) (18).

2.7.5: Pharmacodynamic study

The animal locomotor behavior was monitored using actophotometer. Animals were placed in actophotometer individually, and basal activity score was recorded over the period of 5 min. Each animal was treated with respective drug, and activity score was recorded after 30 min and 1 h.

2.7.6: 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%R.H. for 6 months. The change in appearance, physical characteristics and release behavior of the stored films were investigated from 0-6 months (21).

3. RESULT

3.1: Physicochemical 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 in nature. The physicochemical characterization is shown in Table 2 and 3.

Table No. 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˚C

Table No. 3: Chemical Characterization of bio-material

Sr. 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.

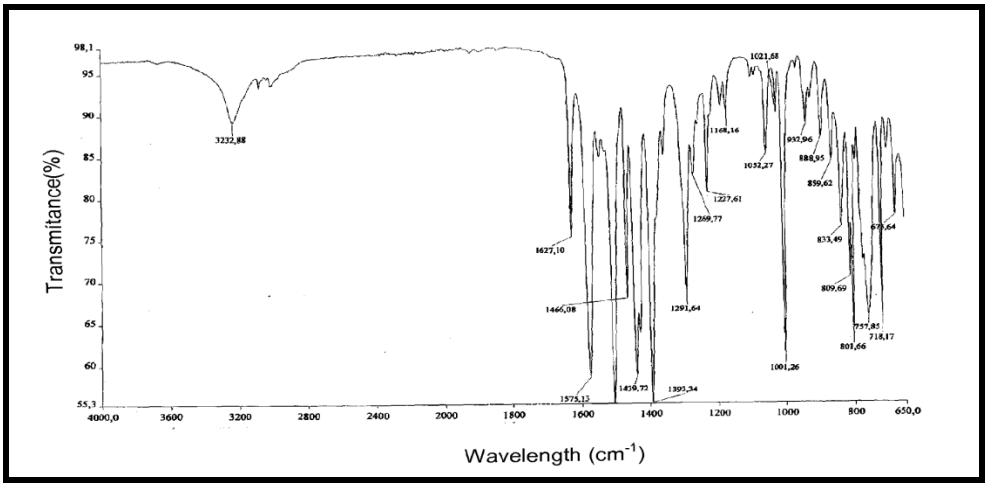

Figure No. 1: IR Spectra of biopolymer isolated from *Zea mays*

The functional groups of bio-material were elucidated by I.R. spectral studies. The IR 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**),1168and 1001 cm^{-1} (**thiocarbonyl**), 932 cm^{-1} (RCO-OH), 757and 718 cm^{-1} (ortho-disub./monosubst./meta-disubstitution) (fig.1). These functional groups confer mucoadhesive property to the biopolymer.

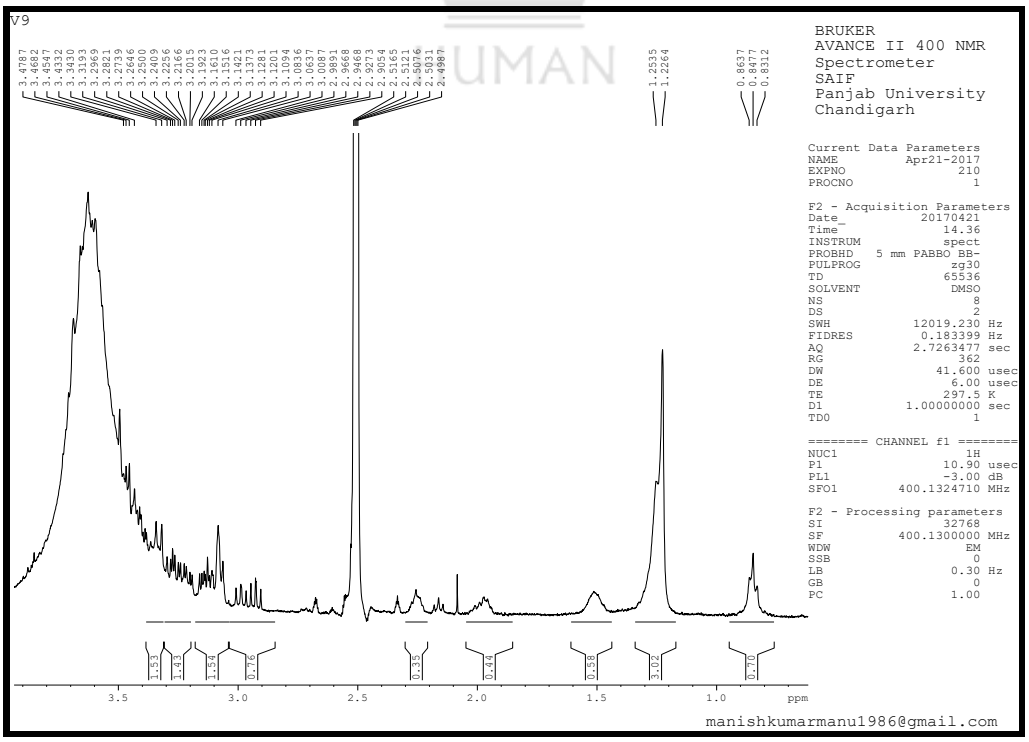

Figure No. 2: 1H-NMR Spectrum of biopolymer isolated from *Zea mays*

Proton NMR spectra of biopolymer depicted the presence of possible groups hydrogen atoms attached to different functional groups viz. RC**H**$_3$ (chemical shift at 0.8477ppm), RC**H**$_2$R (at 1.2535ppm), RC**H**$_2$NH$_2$and ArC**H**$_3$ (at 2.4987 and 2.5165ppm), RC(triple bond)C**H** (at 2.9891ppm), RC**H**$_2$I (at 3.1094 and 3.2969ppm), RC**H**$_2$Br (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 contain oxygen single bonds like alcohols, ethers, or esters.

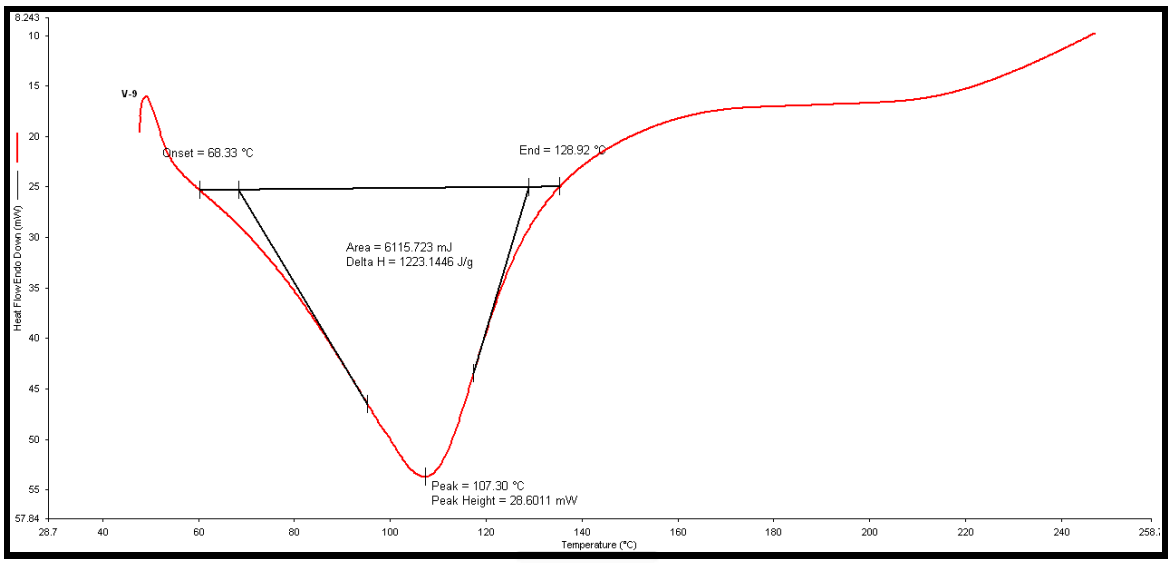

Figure No. 3: DSC Curve of biopolymer isolated from *Zea mays*

DSC analysis measures amount of heat absorbed when the temperature of the sample is raised at a linear rate. The DSC Curve depicts an endothermic peak at 107.30ºC, it is melting point of biomaterial and also shows monotropic transition i.e. solid transition then 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).

3.2: Drug excipients interaction study

The studies revealed that there was no interaction between the drug and the excipients including the bio-polymer. This was confirmed by the result of the thin layer chromatography in which no change was seen in the Rf value. Also, there was no change in the ƛ max and absorbance also. Since excipients doesn't have any reacting group hence selected for further processing. Value which was observed to be 221 nm prior to the test and after the test it was 221 nm hence confirming that there was no interaction between the drug and excipients. It

was concluded that none of the excipients had a deleterious effect on the drug and could be used for the formulation of the flexy-films.

3.3: Nanosizing characterization by High through Put Screening Method

Nanosized particles were evaluated by measuring % Transmittance before and after each cycle of sonication. As the number of sonication cycles was increased there was an increase in the % transmittance indicating that the particles may be gone in nano range thus increasing the transmittance (fig. 4).

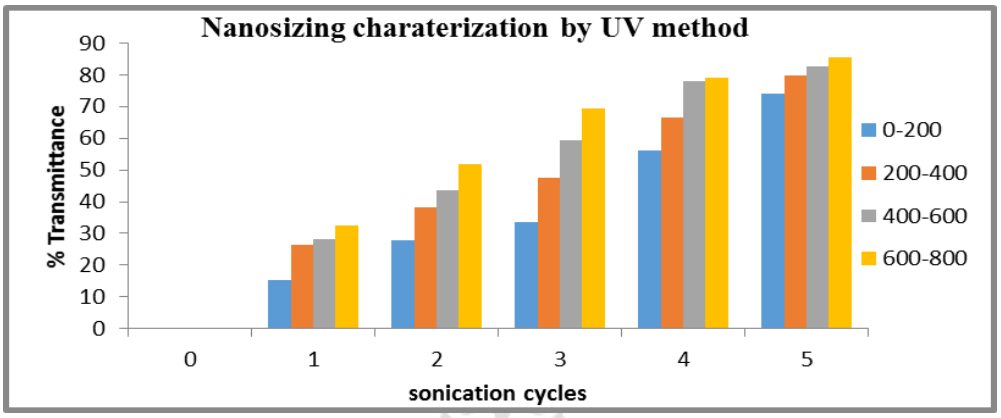

Figure No. 4: Nano sizing characterization by High throughPut Screening Method

3.4: *Ex-vivo* Permeability Study

Drug permeability was assessed by using egg shell membrane as biological membrane. A permeation graph was plotted between concentrations vs. time, depicting the amount of drug permeated through the membrane (fig. 5).

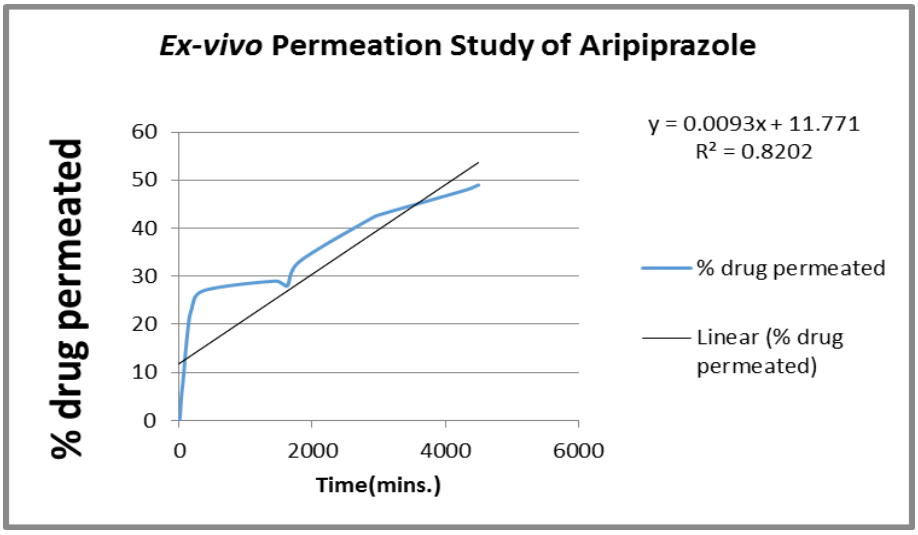

Figure No. 5: *Ex-vivo* Permeation Study of Aripiprazole

3.5: Formulation of nanosized aripiprazole loaded flexy films

Nanosized Aripiprazole loaded bio-flexy films (FZ1-FZ5 and FM1-FM5) were prepared by using biopolymer isolated from *Zea mays* as mucoadhesive strip former, HPMC as standard mucoadhesive polymer, D-glucose as flexicizer and other co-processing agent like 1,2,3-Propanetriol as plasticizer. All the prepared formulations were subjected for different evaluation parameters.

3.6: Evaluation of nanosized aripiprazole loaded flexy films

All flexy films were transparent in nature, smooth and translucent in appearance, thin and flexible in nature. The weight variation and %drug content of all the flexy films was ranged from 31.48- 36.96mg and 98.5-99.3% respectively as depicted in Table 4. All the prepared formulations (FZ1-FZ5 and FM1-FM5) showed folding endurance from 130 times to 161 times as shown in Table 5. Folding endurance study explain that there was increase in the flexibility of the films as the polymeric concentration was increased in the formulations. FZ5 showed maximum folding endurance of 161 times in comparison to other formulations, this may be due to the presence of highest concentration of polymer and flexicizer. FM1 showed minimal folding endurance of 130 time. All the prepared formulations (FZ1-FZ5 and FM1-FM5) showed a surface pH in the range of 7.34 to 7.38 as shown in Table 5 which is near to labial pH and devoid of any irritation as formulations contain biopolymeric substance which is edible, biocompatible, economical and devoid of any mucosal irritant groups.

Table No. 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)
FZ1	7.34± 0.04	32.33± 0.06	98.5± 0.04	132± 05
FZ2	7.34± 0.04	33.54± 0.10	99.2± 0.05	139± 04
FZ3	7.39± 0.03	34.18± 0.08	99.3± 0.05	148± 02
FZ4	7.38± 0.04	35.61± 0.07	99.2± 0.04	153± 06
FZ5	7.38± 0.05	36.96± 0.09	99.3± 0.05	161± 04
FM1	7.38± 0.03	31.48± 0.09	98.9± 0.04	130± 05
FM2	7.40± 0.05	32.27± 0.08	98.9± 0.05	138± 03
FM3	7.39± 0.04	33.48± 0.11	99.1± 0.04	145± 04
FM4	7.41± 0.05	35.06± 0.10	99.2± 0.05	155± 02
FM5	7.38± 0.03	35.98± 0.07	98.7± 0.04	160± 03

3.6.1: Mucoadhesion study

The mucoadhesion of the prepared films was assessed by *ex-vivo* Rotating Cylinder method using goat intestinal mucosa. All the formulations showed significant mucoadhesion time and as the concentration of polymer was increased there was proportional increase in the mucoadhesion time (fig. 6). The *Ex-vivo* mucoadhesion study showed that formulation FZ5 and FM5 had maximum mucoadhesion for a period of 36 and 34hrs respectively. This may be due to presence of mucoadhesive functional groups like carboxylic and hydroxyl and optimized proportion of polymer. FZ2 and FM1 showed least mucoadhesion time of 21 and 24hrs respectively. This may be due to the minimum concentration of biopolymer and/or over dehydration. Upon increasing the biopolymer and standard polymer concentration there was an appreciable increase in the mucoadhesion time.

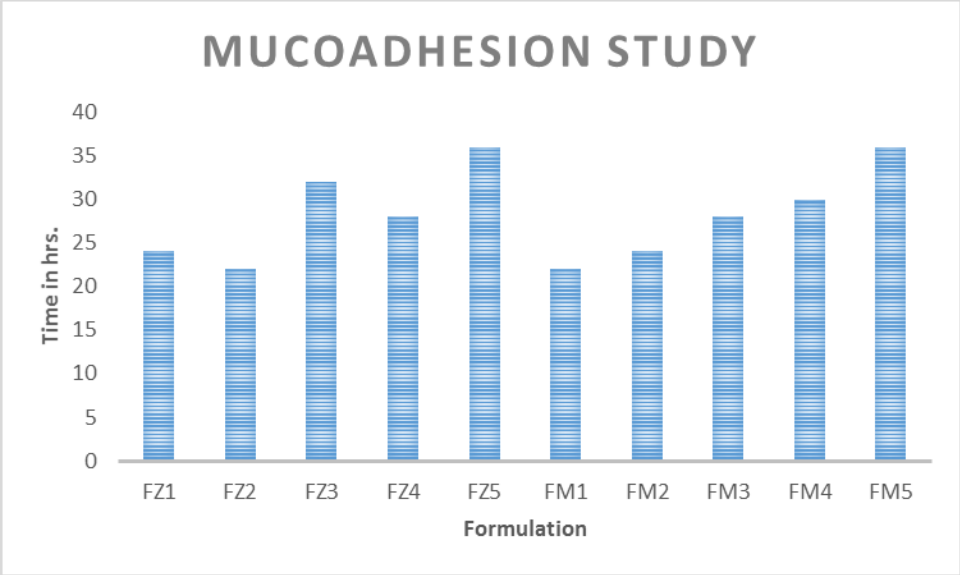

Figure No. 6: *In-vitro* Mucoadhesion Study by Rotating Basket Method

3.6.2: *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. The comparative drug release profile of all the formulations showed that the drug released followed the descending order: FZ3>FM5>FM4>FM3>FZ5>FZ4>FM2>FZ2>FM1>FZ1(fig.7) The *In-Vitro* drug release study revealed that formulation FZ3 showed t50% value 4.5 hrs, and released 94% drug in 24 hrs. Biopolymer showed drug release retardation property and released drug for a longer period of time thus reducing the dosing frequency. Formulation FZ3 followed Peppas

Korsmeyer model with R^2 value 0.9405 and mechanism of drug release was Anomalous Transport.

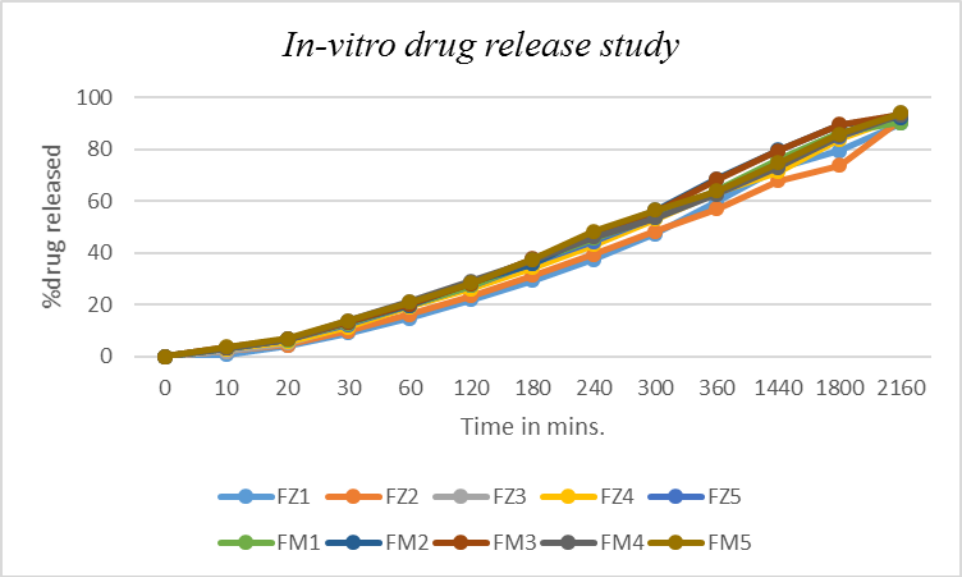

Figure No. 7: *In-vitro* Drug Release Study by Franz Diffusion Cell Apparatus

3.6.3: Pharmacodynamic Study*:*

Decreased activity score was taken as index of CNS depression. The result it is shows that Test formulation FZ3 increases locomotion in depression induced rats as compared to Disease control Haloperidol group (fig. 8).

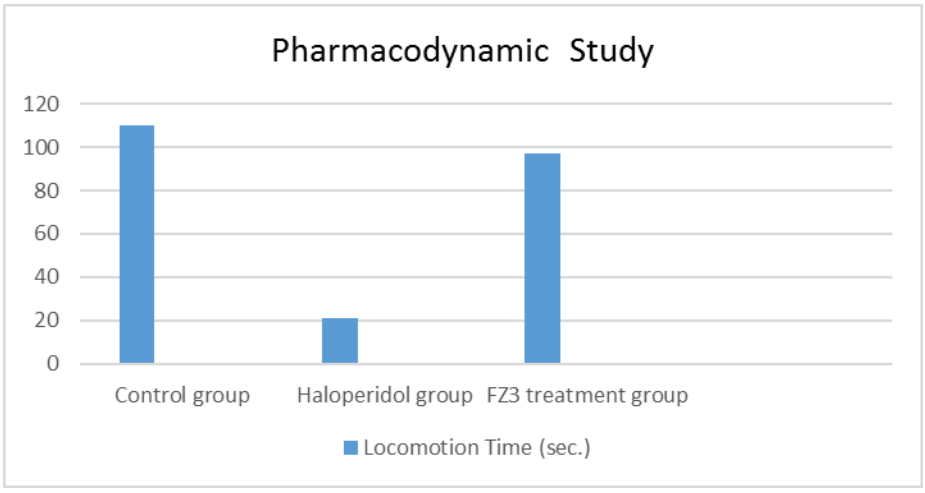

Figure No. 8: Locomotor activity after Aripiprazole loaded film (FZ3) administration

4. DISCUSSION

The spectral analysis and mucoadhesive study results showed that the biopolymer from *Zea mays* can serve as film former and it can be used for designing of various pharmaceutical mucoadhesive dosage forms. The biopolymer safe and economic in use. On comparison of the performance of all flexy films including texture, flexibility, surface pH, weight uniformity, content uniformity, folding endurance, mucoadhesivity, *In-vitro* drug release retardability, the FZ3 formulation was selected as best optimized flexy strip. The best formulation was stable over a period of 6 months as there was no change in the physical appearance, drug content and *In-vitro* release. The pharmacodynamics response showed improvement in locomotor activity in depression induced rats in comparison to haloperidol induced rats.

5. CONCLUSION

In proposed research, an attempt was made to develop nanosized Aripiprazole loaded bio-flexy films for oro-translabial mucosal route. The Bio flexy films of nanosized aripiprazole can be developed for commercialization. Nanosizing offers reduction in dose up to 10 folds there by reducing the dose related serious life threatening adverse effects of aripiprazole in chronic therapy. Hence it can serve as potential dosage form for improved safety, efficacy and patient compliance. The incorporation of mucoadhesive film in the market and their inclusion in European Pharmacopoeia shows its promising results, wide acceptability and potentialities of these dosage forms. The sales of these dosage forms are more than $1.2 billion which also signifies the same and allow to explore other mucoadhesive sites for drug delivery.

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