Development and evaluation of nanosized aripiprazole-loaded bioflexy films using a biopolymer from *Lagenaria siceraria* for brain delivery through orosoft palatal mucosal platform

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Purpose
The National Institute of Mental Health estimated the global cost of mental illness to be $6T by 2030. The purpose of the study was to deliver aripiprazole for brain targeting by suitably designing a bioflexy film for the treatment of different brain disorders.
Materials and methods
Bioflexy films were prepared by solvent casting technique using aripiprazole as a model drug, different concentrations of isolated biopolymer from *Lagenaria siceraria*, and a standard polymer.
Results
All formulations of aripiprazole were flexible, smooth, and transparent in nature, with a weight range from 23.73 to 34.48 mg, pH range from 7.27 to 7.39, and folding endurance of 94–116 times. The content uniformity was in the range of 97.2–98.6.
Conclusion
In-vitro and in-vivo release shows FL2 as the best formulation. On the basis in-vitro and in-vivo drug release, FL2 was found to be best formulation showing mucoadhesivity (36 h), $t_{50\%}$ of 2.5 h, $t_{80\%}$ of 23.4 h, and having R^2 value of 0.9923, best-fit model Higuchi matrix analyzed by BIT-SOFT 1.12. Moreover, it was observed that significant amount of drug reaches to the brain through soft palatal route through neural pathway.

Keywords:
aripiprazole, biofilm former, bioflexy films, brain targeting, lagenaria siceraria

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Introduction

Schizophrenia is a long-term brain disorder affecting more than 21 million people worldwide [1]. A number of drug molecules cannot enter into the brain because of their low lipid solubility and also they are not transported by specific carriers present in the blood–brain barrier [2]. Unfortunately, for this reason, most of the long-term brain diseases like depression, psychosis, autism, and schizophrenia remain untreated yet [3].

Aripiprazole is a second generation atypical antipsychotic that improves both positive and negative symptoms of schizophrenia, that is, depression and mania. These effects are associated with its partial agonistic activity at D2 receptors [4]. Aripiprazole is categorized under black box warning drugs, as it produces suicidal tendencies in specially pediatric and geriatric patients owing to its serious adverse effects. The elderly patients having psychosis when treated with aripiprazole have greater risk of death owing to cardiovascular collapse, infection, or stroke [5].

The soft palatal route is flexible, is highly vascularized, and has nonkeratinized stratified squamous epithelium, and it is supposed to be 4–4000 times more permeable than skin [6]. It is innervated by cranial nerve V (i.e. lesser palatine nerve). The soft palatal delivery offers direct targeting of drug molecule into the brain through interneural and intraneural pathways [7].

The plant *Lagenaria siceraria* (Family: Cucurbitaceae) is commonly known as bottle gourd, is grown throughout the India, and is available in the market whole year. The phytochemistry of plant showed 2.5 g of carbohydrate, 0.2 g of protein, and 0.6 g of fiber per 100 g of edible portion. The fruit also contains vitamin B and ascorbic acid, water soluble polysaccharide, minerals, and amino acids [8].

Drug delivery through orosoft palatal route using bioadhesive dosage form such as bioflexy films is a novel route of drug delivery. Orosoft palatal mucosa is the site for administration of bioflexy films, and

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they adhere to the mucus membrane after hydration by means of different forces [9].

The work on mucoadhesive bioflexy films of aripiprazole is yet not found, hence this is an area of interest. Being developed from a biopolymer that is isolated from a natural edible source, it is economical and safe to use.

The aim of our research work was to isolate a biopolymer from *L. siceraria* and develop and evaluate nanosized aripiprazole-loaded bioflexy films using a biopolymer for brain delivery through orosoft palatal mucosa.

Materials and methods

Aripiprazole was received as a gift sample from Sun Pharma (Mumbai, India). *L. siceraria* was procured from a local market of Dehradun, Uttarakhand, India. Sodium alginate, d-glucose, 1,2,3-propanetriol, and all other chemicals and solvents were of analytical reagent grade.

Isolation of biomaterial from the pulp of *L. siceraria*

A total amount of 250 g of *L. siceraria* was taken, and its outer cover removed. Then it was mixed with 250 ml distilled water in a mixer to get a smooth slurry, and it was filtered through a muslin cloth. The filtrate was centrifuged at 3000 rpm to remove the extraneous matter. The supernatant liquid was treated with optimized quantity of propanone and kept in a refrigerator for 24 h. The biomaterial was separated by centrifugation at 4000 rpm for 25 min. The biomaterial was dried in a desiccator for 48 h. The biomaterial extraction was repeated six times, and practical yield was reported [10].

Physicochemical characterization and spectral analysis of the isolated biomaterial

The isolated biomaterial was tested for various physicochemical properties like color, odor, solubility, color changing point, and chemical tests for carbohydrates (Molisch's test and Benedict's), proteins (biuret test), and starch. Spectral studies like infrared spectra was performed using KBr pellet technique, and sample concentration in the pellet was 1% (Shimadzu IR Tracer-100; Fourier Transform Infrared Spectrophotometer) by Shimadzu.

In-vitro mucoadhesivity study of isolated biopolymer

The isolated biopolymers were screened for mucoadhesivity. The films were prepared in the ratios of 1–5% w/v biopolymer from *L. siceraria*. The biopolymer was accurately weighed in different ratios and triturated with 10 µl of 1,2,3-propanetriol, and 80 mg of d-glucose as flexicizer. Overall, 10 ml of distilled water added into it and subjected to mechanical stirring for 30 min. The resulting solution was poured onto a Petri dish for natural drying for ~24 h. The dried bioflexy films were tested for mucoadhesivity by rotating cylinder method using type II dissolution apparatus on a 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 100 rpm in 900 ml of pH buffer 7.4 at 37°C. The films were observed at different time intervals, and the time required for dislodgement and/or disintegration was recorded [11].

Drug excipients interaction study

The drug interaction study was performed using wet and dry method. The drug was physically mixed with excipients in dry method, and in 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 a period of 3 days. Both the mixtures were dissolved in methanol and then analyzed by thin-layer chromatography and ultraviolet (UV) spectrophotometric method at 221 nm [12].

Formulation of nanosized aripiprazole-loaded flexy films

Aripiprazole was nanosized by using novel method. The drug was dissolved in a suitable solvent, and 10 µl of 1,2,3-propanetriol was added as nanosizant into it. As water is the most beneficial solvent, it will be of interest to study the effect of water in propanetriol on the formation of nanoparticles. Propanetriol has the ability to enhance the wettability of aripiprazole and serves as a good dispersing agent, which aids in nanosizing of the particle, hence it acts as a nanosizant [13].

Overall, 10 ml of distilled water was added into it and sonicated for five cycles (each cycle of 3 min). The solution was microcentrifuged at 10,000 rpm for 15 min, and the residue was dried and collected. Nanosized aripiprazole-loaded flexy films, using biopolymer and a standard polymer, that is, sodium alginate, were prepared by using 'solvent casting method' [14]. In this method, biopolymer from *L. siceraria* and sodium alginate was accurately weighed in different ratios and triturated with 10 µl of 1,2,3-propanetriol and 80 mg of d-glucose as flexicizer. Moreover, 10 ml of distilled water added into it and subjected to mechanical stirring for 30 min. In addition, 10 mg of drug was dissolved separately in

ethanol. The nanosized drug solution was added to the polymeric solution under stirring at 4500 rpm. The polymeric solution was poured onto a Petri dish for natural drying of ~24 h (Tables 1 and 2).

Evaluation of nanosized aripiprazole-loaded flexy films

Nanosizing characterization by ultraviolet spectroscopic method

It is a novel preliminary screening method for nanosizing range of particles by UV spectroscopy and performed after each cycle of sonication. Transmittance is based on the concept of Tyndall effect. When a light passes through a medium or solution that does not contain solute between 200 and 400 nm size range, 100% light gets transmitted. If a solvent contains any solute particles ranging 200–800 nm, then the particles may absorb a light and proportionally show absorbance by reducing the t=0.05% by reducing/blocking 10% of absorbance and 90% of transmittance similarly 1% absorbance with t=10 and 90% blockage [15].

Appearance, weight uniformity, and content uniformity study

All the flexy films were weighed three times and 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 flask were stirred for 4 h on magnetic stirrer. The drug content was then determined after appropriate dilutions by using a UV spectrophotometer (Shimadzu 1800) [11].

The drug content was calculated by using the following equation:Eq. (1)

$$\text{Drug content} = \frac{\text{Analyzed content}}{\text{Theoretical content}} \times 100.$$

Folding endurance and surface pH

The selected films were subjected to repeatedly folding a film (area 4 cm^2) at the same place until it broke, and the number of foldings was recorded. The surface pH of flexy films was measured by using pH meter [11].

Mucoadhesion study

The mucoadhesive property of prepared films was evaluated by rotating cylinder method using goat soft palatal mucosa with phosphate buffer pH 7.4. After each 30 min and up to 36 h, the film was observed for any dislodgement or disintegration from the soft palatal mucosal surface. The results were compared with the standard films of sodium alginate [11].

In-vitro drug release study

The in-vitro drug diffusion was carried out by using the dynamic Franz diffusion cell method. Egg shell membrane was tied onto the donor compartment, and flexy film of 1 cm^2 area was kept on above the membrane, and the receiver compartment were filled with 7 ml of phosphate buffer pH 7.4. A 4 ml sample was withdrawn at the intervals of 0, 10, 20, 30, 60, 120, 180, 300, 360, 480, and 1440 min and replaced with 4 ml of fresh medium. The amount of drug released was assessed by measuring the absorbance at 221 nm using UV spectrophotometer (Shimadzu 1800) [11,12].

In-vivo study

Animal experiment was done with the permission of institutional ethical committee. The rabbits were divided into two groups – test and control – and each group contains two rabbits. All rabbits were kept in separate cages and maintained at 25°C

Table 1 Formulation of aripiprazole-loaded bioflexy films of *Lagenaria siceraria*

Formulations	FL1 (1 : 1)	FL2 (1 : 2)	FL3 (1 : 3)	FL4 (1 : 4)	FL5 (1 : 5)
Aripiprazole (mg)	10	10	10	10	10
Lagenaria siceraria (mg) (%)	1	2	3	4	5
d-Glucose (mg)	80	80	80	80	80
1,2,3-Propanetriol (µl)	10	10	10	10	10
Distilled water (ml)	10	10	10	10	10

Table 2 Formulation of aripiprazole-loaded flexy films of sodium alginate as film former

Formulations	FA1 (1 : 1)	FA2 (1 : 2)	FA3 (1 : 3)	FA4 (1 : 4)	FA5 (1 : 5)
Aripiprazole (mg)	10	10	10	10	10
Sodium alginate (mg) (%)	1	2	3	4	5
d-Glucose (mg)	80	80	80	80	80
1,2,3-Propanetriol (µl)	10	10	10	10	10
Distilled water (ml)	10	10	10	10	10

and 70% relative humidity. The animals were housed under standard laboratory conditions, maintained under light and dark cycle of 12 h in light and 12 h in dark, and had free access to food and water. The flexy film containing 10 mg of aripiprazole was applied onto the soft palatal mucosa of test group for a period of 72 h. The blood samples were collected at 0, 1, 3, 6, 12, 24, 48, and 72 h.

Pharmacodynamic study

The pharmacodynamic study was performed by monitoring locomotor activity of Wistar albino rats using actophotometer. Rats were divided into two groups – test group (group I) and control group (group II) – each group containing three rats. Animals were maintained under light and dark cycle of 12 h in light and 12 h in dark under 25°C and 70% relative humidity. Animals were placed in the actophotometer individually, and basal activity score was recorded over a period of 5 min. Then the flexy film containing 10 mg of aripiprazole was applied onto the soft palatal mucosa of test group, and the activity score was recorded after 30 min and 1 h [16].

Stability study

Optimized best flexy film was subjected to stability study as per International Council for Harmonization guidelines. The film were kept in an incubator (stability study chamber) and maintained at 37±5°C and 75±5% RH for 6 months. The changes in appearance, physical characteristics, and release behavior of the stored films were investigated from 0 to 6 months [14].

Results

Isolation, physicochemical characterization, and spectral analysis of isolated biomaterial from *L. Siceraria*

The percentage yield of *L. siceraria* was found to be 14.8± 3.12%. The isolated biomaterial is carbohydrate and proteinaceous in nature. The physicochemical characterization is shown in Table 3. The biomaterial was purified by hot dialysis method, and it was devoid of chlorides and sulfates. The functional groups of biomaterial were elucidated by IR spectral studies.

Table 3 Characterization of biomaterial

Tests	Observation	Inference
Molisch	+	Carbohydrate present
Benedict	+	Carbohydrate present
Biuret	+	Proteins present
Color	Green	
Odor	Characteristic	
Taste	Characteristic	
Solubility	Slightly soluble in water	
Melting point	267±10°C	

The IR spectral interpretation by IR Pal V. 2.0 reported the presence of alkanes and alkenes (2923 cm^{-1}), carboxylic acids (2831 cm^{-1}), esters (1736 cm^{-1}), alkanes (1465 cm^{-1}), and thiocarbonyl (1172 cm^{-1}) (Fig. 1). These functional groups are responsible for the mucoadhesive property of the biopolymer. These functional groups are somewhat similar, which are present in other standard mucoadhesive polymers like PEG 400 and Carbopol 974.

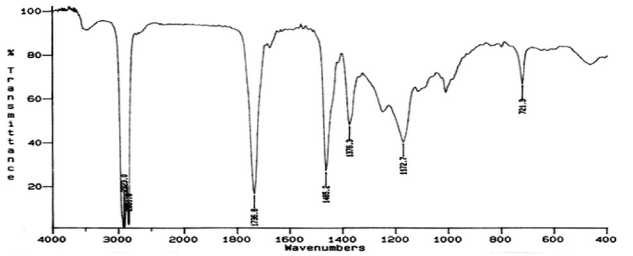
In-vitro mucoadhesivity study of isolated biopolymer

The isolated biopolymer showed maximum mucoadhesion time of 36 h at the concentration of 5%. The results revealed that as the concentration of biopolymer was increased, there was also an increase in mucoadhesion time, which can be useful for designing mucoadhesive dosage form (Fig. 2).

Drug excipients interaction study

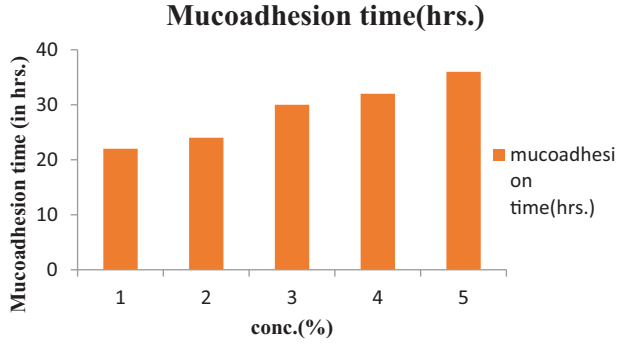
The studies revealed that there was no interaction between the drug and the excipients including the biopolymer. This was confirmed by the result of the thin-layer chromatography in which no change was seen in the retardation factor value. There was no change in the $?_{max}$ and absorbance also. This

Figure 1



Infrared spectra of *Lagenaria siceraria*.

Figure 2



In-vitro mucoadhesion study of isolated biopolymer.

resulted because excipients do not have any reacting group, hence they were selected for further processing. The value that was observed to be 221 nm before the test, 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.

Evaluation of prepared nanosized aripiprazole-loaded flexy films

Nanosizing characterization by ultraviolet spectroscopic method

Percentage transmittance was measured before and after each cycle of sonication. As the number of sonication cycles was increased, there was an increase in the percentage transmittance, indicating that the particles may be gone in nano range, thus increasing the transmittance (Fig. 3).

Appearance, weight uniformity, and content uniformity study

All flexy films were transparent in nature, smooth in appearance, and flexible in nature. The weight variation and percentage of drug content of all the flexy film formulas were in the range of 23.73–34.48 mg and 97.2–98.6%, respectively, as shown in Table 4.

Folding endurance and surface pH

The results were shown in Table 4. All the prepared formulations (FL1–FL5 and FA1–FA5) showed folding endurance in the range of 94–117 times. The surface pH of all the formulations was approximately nearer to the pH of the mucosal membrane, which means that all the formulations are nonirritant to soft palatal mucosa.

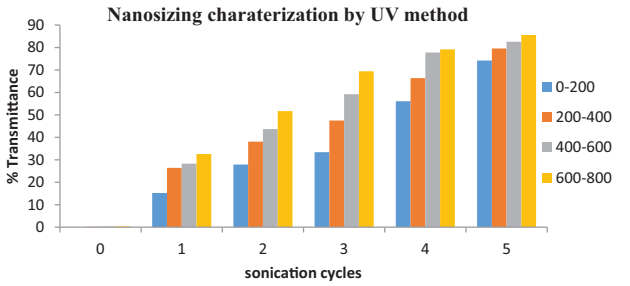
Mucoadhesion study

The mucoadhesion of the prepared films was assessed by in-vitro rotating cylinder method using goat soft palatal mucosa. All the formulations showed significant mucoadhesion time, whereas formulation FL2, FL5, FA3, and FA5 showed maximum contact time (36 h) and FL1, FL3, FA1, and FA2 showed mucoadhesion time of 24 h on palatal mucosa (Fig. 4). On comparison of mucoadhesion time of all 10 formulations, the following ascending order was observed: FL1<FA1<FA2<FL3<FL4<FA4<FL2<FL5<FA3<FA5.

In-vitro drug release study

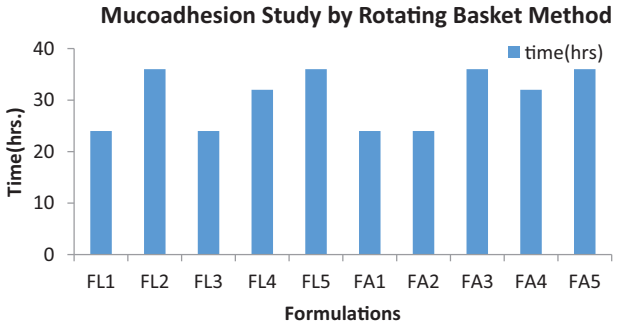
The in-vitro drug release kinetics was analyzed by BIT-SOFTWARE. The $t_{50\%}$ and $t_{80\%}$ of formulations were calculated and reported. The

Figure 3



Nanosizing characterization by ultraviolet spectroscopic method.

Figure 4



In-vitro mucoadhesion study by rotating cylinder method.

Table 4 The pH, weight, folding endurance, and percent of drug content in aripiprazole-loaded flexy film formulations

Formulation codes	pH	Weight uniformity (mg)	Folding endurance (times)	% Drug content
FL1	7.34±0.05	23.89±0.07	110±0.5	96.3±0.04
FL2	7.32±0.07	27.54±0.04	116±0.6	98.9±0.03
FL3	7.32±0.08	28.73±0.07	114±0.4	97.1±0.08
FL4	7.39±0.06	32.71±0.06	117±0.2	96.7±0.07
FL5	7.31±0.05	33.98±0.08	114±0.3	97.8±0.05
FA1	7.27±0.04	23.73±0.03	94±0.7	98.3±0.06
FA2	7.29±0.06	29.56±0.04	112±0.2	97.5±0.04
FA3	7.35±0.05	32.78±0.06	106±0.3	98.4±0.04
FA4	7.37±0.06	33.01±0.05	111±0.4	95.8±0.02
FA5	7.36±0.07	34.48±0.04	114±0.5	97.2±0.04

in-vitro drug release study revealed that formulation FL2 had $t_{50\%}$ at 3.9 h, $t_{80\%}$ at 24 h, and maximum drug release of 81.01%.

The comparative drug release profile of all the formulations showed that the drug released followed the descending order: FL2>FA1>FL4>FA5>FL5 >FA3>FL1>FL3>FA4>FA2 (Fig. 5).

In-vivo study

Formulation FL2 and FA2 were selected for in-vivo studies based on the aforementioned parameters. The in-vivo studies revealed that significant amount of drug was released in a period of 75 h. The area under the curve reported the C_{max} was 192.78 ng/ml and t_{max} was 48 h (Fig. 6).

Pharmacodynamic study

The photoactometer study showed the evidence of central nervous system stimulation by the drug-loaded flexy film application in rats of group I in the form of increased activity score. However, the rats in the control group, that is, group II, did not show comparable increase in activity score (Fig. 7).

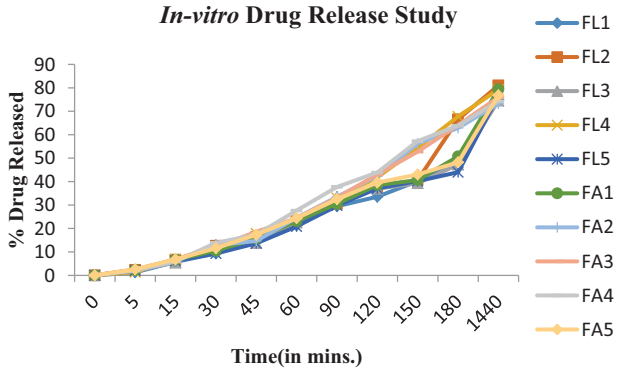
Stability study

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.

Discussion

A total of 10 nanosized aripiprazole-loaded bioflexy films (FL1–FL5 and FA1–FA5) were prepared by using biopolymer isolated from *L. siceraria* as a film former, sodium alginate as a standard polymer, d-glucose as flexicizer, and other coprocessing agent like 1,2,3-propanetriol as plasticizer.

Figure 5



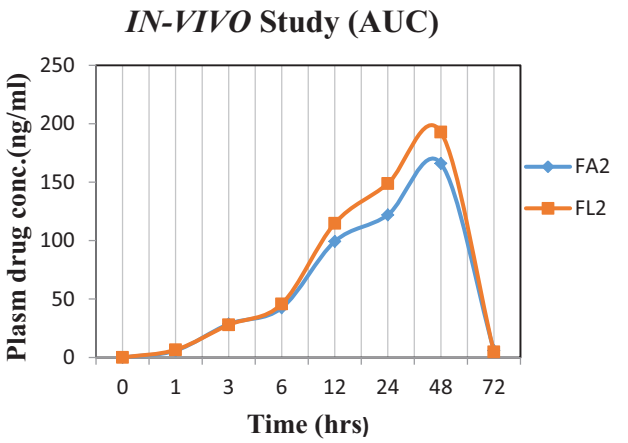
In-vitro drug release study by Franz diffusion cell apparatus.

All the prepared formulations were subjected for evaluation parameters. All the prepared formulations (FL1–FL5 and FA1–FA5) showed a surface pH in the range of 7.27–7.39, which is near to neutral in nature and devoid of irritation, as formulations were prepared by using a biopolymeric substance that is edible, biocompatible, economical, and devoid of any mucosal irritant groups. Hence, it showed neutral bioflexy films.

Folding endurance study revealed that there was a slight increase in the flexibility of the films as the polymeric concentration was increased in the formulations FL2, FA2, FA4, and FA5, and the flexibility was slightly decreased in the formulations FL3, FL5, FL3, and FL4. FL3 and FA5 showed similar folding endurance. FL2 showed maximum folding endurance of 116 times in comparison with other formulations; this may be because of the presence of flexicizer.

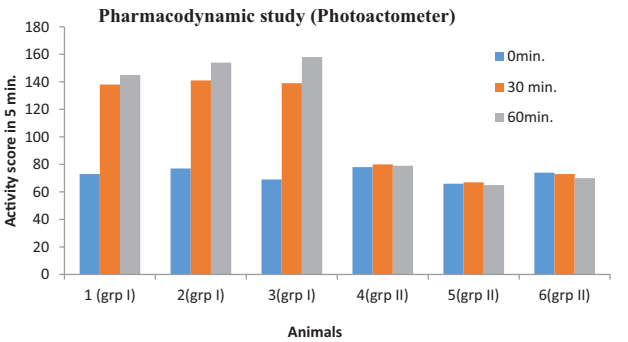
The in-vitro mucoadhesion study showed that formulation FL2 had mucoadhesion for a period of

Figure 6



In-vivo drug study. AUC, area under the curve.

Figure 7



Pharmacodynamic study by photoactometer.

36 h. This may be because of presence of functional groups like carboxylic and thiocarbonyl and optimized proportion of flexicizer and plasticizer. Similar results were shown by FL5, but FL2 was selected as the best flexy film, containing minimum amount of biopolymer and having maximum mucoadhesion time. FL4 and FA4 showed a mucoadhesion property over a period of 32 h. On increasing the biopolymer and standard polymer concentration, there was a slight reduction in the mucoadhesivity; this may be owing to the excess hydration of biopolymer. Formulation FA1 showed minimum mucoadhesion time of 94 h; this may be because of the minimum concentration of biopolymer and/or overdehydration.

In-vitro drug-release profile showed that with further increase in the concentration of biopolymer in flexy films, the drug release retardation was reduced slightly, as this may because of more uptake of water by the prepared film during release study, and enhancing the porosity of film may lead to the reason for aforementioned release performance.

On comparison of the performance of all flexy films including texture, flexibility, surface pH, weight uniformity, content uniformity, folding endurance, mucoadhesivity, and in-vitro drug release retardibility, the FL2 formulation was selected as the best optimized film.

The results of in-vivo study showed area under the curve of 9253.44 ng h/ml, indicating that aripiprazole can enter the blood circulation through soft palatal mucosa, hence it can serve as a drug delivery platform. There was an increase in the locomotor activity of experimental animals (group I) after flexy film application, which signifies the increased central nervous system activity.

Conclusion

Aripiprazole can be effectively delivered by administering optimized bioflexy films prepared using biopolymer from *L. siceraria* and other coprocessing agents. The prepared films can be used for orotrans soft palatal mucosal route. The formulations showed an increase in activity score in experimental animals as the drug may reach to the brain region through intraneural and interneural pathway and systemically to the brain region through blood–brain barrier because of the presence of nanosized aripiprazole moiety in the formulation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 World Health Organization. April 2016. http://www.who.int/entity/mediacentre/factsheets/fs396/en/. [Accessed 17 May 2016].

2 Rautio J, Laine K, Gynther M, Savolainen J. Prodrug approaches for CNS delivery. AAPS J 2008; 10:92–102.

3 Neuwelt E, Abbott NJ, Abrey L, Banks WA, Blakley B, Davis T, *et al.* Strategies to advance translational research into brain barriers. Lancet Neurol 2008; 7:84–96.

4 Tanahashi S, Yamamura S, Nakagawa M, Motomura E, Okada M. Dopamine D2 and serotonin 5-HT1A receptors mediate the actions of Aripiprazole in mesocortical and mesoaccumbens transmission. Neuropharmacology 2012; 62:765–774.

5 Kalinichev M, Rourke C, Daniels AJ, Grizzle MK, Britt CS, Ignar DM, Jones DN. Characterisation of olanzapine-induced weight gain and effect of Aripiprazole vs olanzapine on body weight and prolactin secretion in female rats. Psychopharmacology 2005; 182: 220–231.

6 Umashankar MS, Madhav NVS. A smart oro-soft palate mucosal drug delivery: credentials and future trends. Marmara Pharm J 2015; 19: 208–221.

7 Shakya P, Madhav NVS, Shakya AK, Singh K. Palatal mucosa as a route for systemic drug delivery: a review. J Control Release 2011; 151:2–9.

8 Kumar A, Partap S, Sharma NK, Jha KK. Ethnobotanical and pharmacological profile of *lagenaria siceraria* – a review. J Pharmacogn Phytochem 2012; 1:24–31.

9 Gawas SM, Dev A, Deshmukh G, Rathod S. Current approaches in buccal drug delivery system. Pharm Biol Eval 2016; 3:165–177.

10 Madhav NVS, Shankar MSU. A novel smart mucoadhesive biomaterial from *Lallimantia royalena* seed coat. J Science Asia 2011; 37:69–71.

11 Madhav NVS, Yadav AP. A novel translabial platform utilizing bioexcipients from *Litchi chinensis* for the delivery of rosiglitazone maleate. Acta Pharm Sin B 2013; 3:408–415.

12 Kalaichelv R, Thangabalan B, Rao DS, Jayachandran E. UV spectrophotometric determination of Aripiprazole in bulk and pharmaceutical formulation. Eur J Chem. 2009; 6(Suppl 1): S87–S90.

13 Nalawade P, Mukherjee T, Kapoor S. Green synthesis of gold nanoparticles using glycerol as a reducing agent. Adv Nanopart 2013; 2:78–86.

14 Ezhumalai K, Ilavarsan P, Mugundhan RM, Sathiyaraj U, Rajalakshmi AN. Transdermal patches in novel drug delivery system. Int J Pharm Technol 2011; 3:2402–2419.

15 Raina D, Madhav NVS. A smart Bioretardant from Piper betle L. as a co-processing agent used in chlorpromazine bio-nano gel for brain specificity via nasal mucosa. Pharmbit 2014; XXX:33–40.

16 Bhosale UA, Yegnanarayan R, Pophale PD, Zambare MR, Somani RS. Study of central nervous system depressant and behavioral activity of an ethanol extract of Achyranthes aspera (Agadha) in different animal models. Int J Appl Basic Med Res 2011; 1: 104–108.