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Research Article

A NOVEL APPROACH FOR DELIVERY OF RISPERIDONE USING *EURYALE FEROX* BIOPOLYMER FOR TRANSVERMILLION DELIVERY FOR THE MANAGEMENT OF PSYCHOSIS

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ABSTRACT

Objective: The purpose of the present study was to formulate and evaluate risperidone loaded bioflexi films for effective treatment of psychosis. For the preparation of bioflexi films, biopolymer was isolated from seeds of *Euryale ferox* (family Nymphaeaceae) by an economic method. The biopolymer recovered from the concentrate was subjected for various physiochemical properties such as color, solubility, color changing point, and chemical test.

Methods: The bioflexi films were prepared using this biopolymer, dextrose as flexicizer, and sween 80 as permeation enhancer in methanol and water as solvent system.

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 patches 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 Fourier transform infrared spectroscopic technique. *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 was 99.81% with formulation EF3. *In vitro* skin permeation study was also conducted in a modified Franz's diffusion cell which shows that the maximum permeation with the formulation EF3 and it was 768.50 µg/cm^2 after 24 h.

Conclusion: Optimized formulations were found to be suitable for formulating in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and biopolymer used.

Keywords: Bioflexi film, Risperidone, Translabial, *Euryale ferox.*

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INTRODUCTION

Translabial delivery constitutes one of the most important routes for new drug delivery system. Translabial delivery of drugs offers several advantages over conventional delivery including oral and injection methods. Translabial delivery, that traditionally uses a patch containing drug substances pressed onto the lip skin, is non-invasive, convenient, and painless, and can avoid gastrointestinal toxicity (e.g., ulcer diseases) and the hepatic first-pass metabolism [1].

Autism has been one of the major diseases affecting children's in today scenario [2]. Risperidone, an antipsychotic drug, is supposed to be effective in treating behavioral disturbances in children with autism spectrum disorder (ASD). At present, risperidone is administered orally or by injection. It is usually administered as one or two daily oral dose, for an overall dosage of 4–16 mg/day [3].

The low-dose risperidone maintenance therapy is required to control the ASD in children's and long-term prophylactic [13] treatment is needed to prevent relapses. Long-acting modified dosage forms of risperidone are going to be effective in patients and can help in addressing the problem of poor patient compliance [15]. The use of this drug in the lowest possible effective dosage is recommended for minimizing the risk of major side effects. Based on these hypotheses, a rate controlling bioflexi translabial drug delivery system was developed [16].

Simple drug-loaded rate controlling bioflexi film of translabial drug delivery system for risperidone was designed for prolonged period of maintenance therapy instead of conventional dosage form [14]. Moreover, the physicochemical characteristics of risperidone also comply with the general requirement for designing translabial drug delivery system to a good extent [4].

This study search and investigation are expected to add extensively to the existing knowledge and information in the field of proper drug regimen and maintenance therapy of ASD with rate controlling bioflexi films of risperidone. The major problem of transdermal drug delivery system is with the barrier properties of stratum corneum. Thus, the transport across the skin membrane is a complex phenomenon. Therefore, lip skin being the thinnest and richly supplied through blood vessels due to which our lips appear red in color could serve as a novel route for drug delivery. The translabial application of drugs provides several benefits including the avoidance of hepatic first-pass metabolism and ability to provide nearly constant drug delivery over a long period which may reduce systemic adverse effects. Moreover, mucoadhesion studies were also conducted in an effort to understand drug distribution in the patches and the permeation of drug through skin [5].

METHODS

Risperidone was received as a gift sample from Neuro Lifecare, Baddi, Himachal Pradesh. All other chemicals used in the study were of analytical grade.

Development of bioflexi films

A polymeric solution (3% w/v) was prepared by dissolving *Euryale ferox* with risperidone (20% w/w of dry weight of polymer), dextrose as a plasticizer, and sween-80 as a permeation enhancer in methanol:water (1:1) as a solvent system.

First, the solution was prepared with different ratios of polymeric blend without adding sween-80 as a permeation enhancer. The composition of prepared bioflexi film is given in Table 1. Then again, the films were developed using the procedure mentioned above on adding one drop of sween-80 and stirred for 45 min on magnetic stirrer to accomplish homogeneous mixture. After mixing the drug and polymer, solution was allowed to stand for 15 min to remove air bubbles and the solution is poured in the Petri dish. The solvent was allowed to evaporate at 40°C for 24 h to achieve drug-polymer bioflexi film. After 24 h, the film was collected and stored in desiccators until further use.

Evaluation of bioflexi films

Uniformity of weight

Ten different films from individual batches were weighed individually and the average weight was calculated; the individual weight should not deviate significantly from the average weight [6].

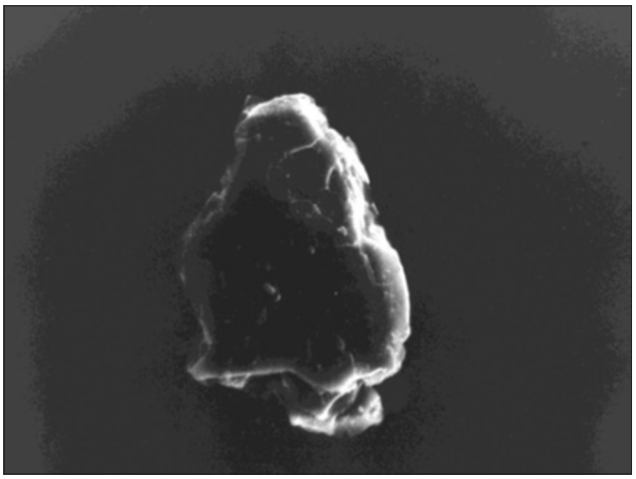

Fig. 1: Scanning electron microscopy image showing risperidone drug particle in bioflexi film

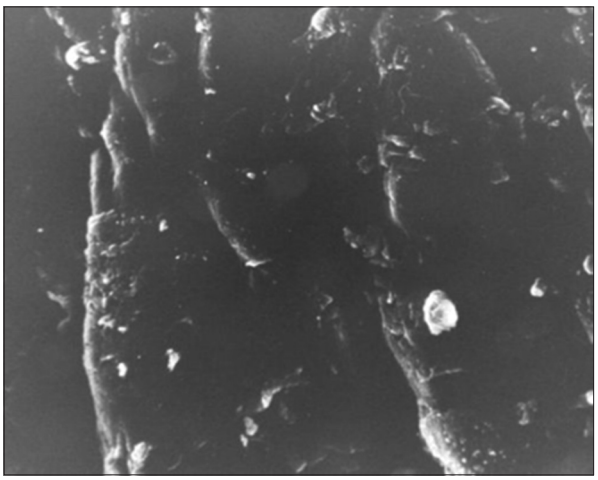

Fig. 2: Scanning electron microscopy image showing bioflexi film after release

Drug content determination

An accurately weighed portion of film was dissolved in 100 mL of methanol in which drug is soluble and then the solution was shaken continuously for 24 h in a mechanical shaker. Then, the whole solution was sonicated. After sonication, drug in solution was estimated spectrophotometrically by dilution [7].

Folding endurance

The film was cut evenly and repeatedly folded at same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance [8].

Thickness of the film

The thickness of the drug-loaded film was measured at five different points using Vernier caliper. The average and standard deviation of five readings were calculated for each batch of drug-loaded films [9].

In vitro release studies

It is needed to maintain greater drug concentrations at the lip skin than in the body. This is required to achieve a constant rate of permeation. The permeation study using Franz diffusion cell with a capacity of 35 mL carried out at 32°C ± 0.5°C. A section of film was cut and placed in donor compartment keeping backing membrane on the upper side. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. Phosphate saline buffer of pH 7.4 with 0.5% sween-80 was used as a media for permeation studies. A similar set was run simultaneously without using the film at the donor compartment egg membrane as a control. The samples were withdrawn at different time intervals and replaced with equal amount of dissolution media and then analyzed using a UV spectrophotometer at 322 nm [10].

In vitro permeation studies

The *in vitro* permeation studies were carried out in a Franz diffusion cell with a capacity of 35 mL, using eggshell membrane. A section of eggshell membrane was cut and placed in the donor compartment, and the film was placed on the membrane. The holder, containing the egg membrane and the formulation, was placed on the receiver compartment of the cell containing phosphate saline buffer of pH 7.4 with 0.5% sween-80. The temperature of the cell was maintained at 32°C ± 5°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar set was run simultaneously without using the patch at the donor compartment as a skin control. The samples were withdrawn at different time intervals and replaced with equal amount of dissolution media. Samples were analyzed spectrophotometrically at 322 nm and the amount of drug permeated per cm^2 of patch was calculated from the standard curve and plotted against time. The difference between the readings of drug skin permeation and skin control was used as the actual reading in each case [11].

Scanning electron microscopy

The morphology of the bioflexi film was analyzed using a scanning electron microscope. The section of the film was cut and mounted on

Table 1: Composition of bioflexi films

Ingredient	EF1	EF2	EF3	EF4	EF5	EF6	EF7	HPMC
Risperidone (mg)	20	20	20	20	20	20	20	20
Euryale Ferox (biopolymer) (mg)	100	200	300	400	500	600	700	200
Dextrose (mg)	80	80	80	80	80	80	80	80
Glycerine (mL)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sween 80 (mL)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Double distilled water (mL)	20	20	20	20	20	20	20	20

HPMC: Hydroxy propyl methyl cellulose, EF: Euryale ferox

stubs using an adhesive tape Figs. 1 and 2. The samples placed on the stubs were coated with gold-palladium alloy using a fine coat ion sputter (JOEL, Fine Coat Ion Sputter JFC-1100). The sections were examined under scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan) [12].

Table 2: Evaluation of transdermal patch for uniformity of weight (mg), drug content, flatness, folding endurance, and thickness (mm)

Formulation code	Uniformity of weight	Drug content (%)	Flatness (%)	Folding endurance	Thickness
EF1	160±0.816	73.90±2.619	100	117.67±1.247	0.32±0.025
EF2	172±1.632	89.65±2.043	100	130.67±0.942	0.41±0.020
EF3	179.67±1.249	88.67±0.845	100	153.67±2.054	0.52±0.026
EF4	190.33±2.054	97.35±0.830	100	184±1.632	0.67±0.033
EF5	196.67±1.247	70.85±0.455	100	191±2.160	0.87±0.021
EF6	207.33±2.054	64.76±6.033	100	208.33±6.236	1.03±0.074
EF7	215±2.449	72.41±1.683	100	183.33±5.436	1.08±0.066
HPMC	176±2.160	90.71±0.490	100	81.33±1.247	0.41±0.005

HPMC: Hydroxy propyl methyl cellulose, EF: Euryale ferox

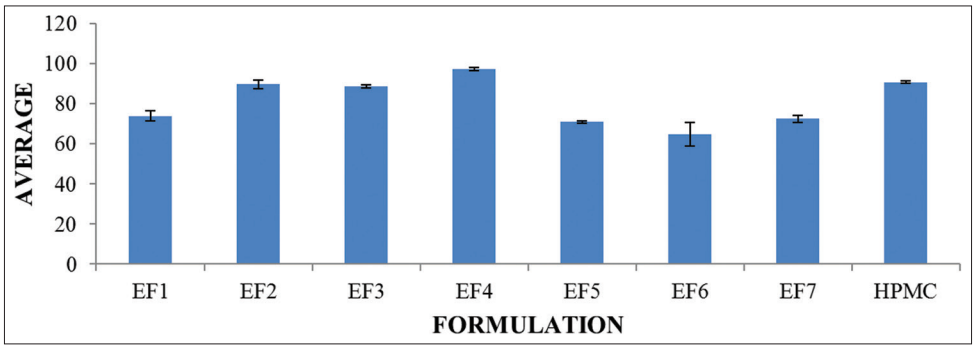

Fig. 3: Drug content of prepared bioflexi films using a different ratio of *Euryale ferox* mean (n = 3) ± standard deviation

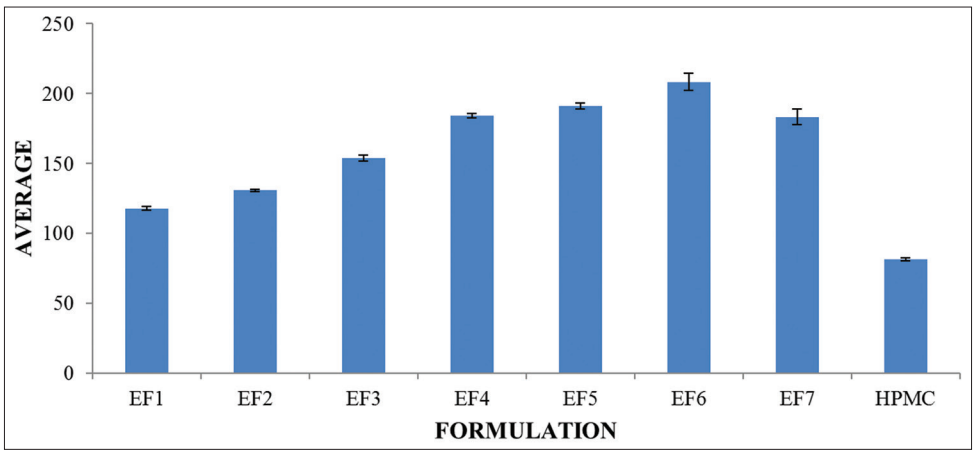

Fig. 4: Folding endurance of prepared bioflexi films using a different ratio of *Euryale ferox* mean (n = 3) ± standard deviation

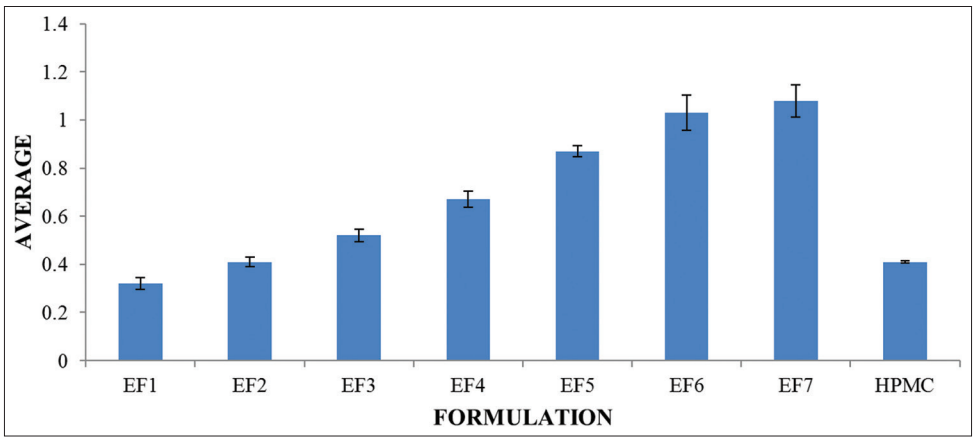

Fig. 5: Thickness of prepared bioflexi films using a different ratio of *Euryale ferox* mean (n = 3) ± standard deviation

RESULTS AND DISCUSSION

A total of 35 formulations were prepared using *E. ferox* and HPMC polymers as per given formula in Table 1. All the films were evaluated for their physicochemical parameters, and they were found to be transparent, smooth, and flexible. They were also found to be uniform in their weight and thickness with low SD values, as shown in Table 2 and Figs. 3-5. A transdermal patch should possess a smooth surface and should not constrict with time. No constriction was observed in any of the prepared formulations; all the surfaces were 100% flat (Table 2). Fourier transform infrared was carried out to check the interaction between the drug Fig. 6 and excipients Fig. 7. Graphs of drug and drug excipients confirmed that there is no interaction between the drug and excipients used Fig. 8.

In vitro release and permeation studies

Drug release from polymer matrix and drug dissolution ensured sustained reproducibility of rate and duration of drug release. Dissolution studies for different formulations were carried out using modified USP paddle-type apparatus using PBS 7.4 with 0.5% tween 80 as dissolution fluid at 32°C ± 0.5°C. The *in vitro* studies of the formulations (EF1 to EF7) and the standard polymer HPMC were shown. All the formulations released >90% of drug within 10 h. Formulation EF3 showed the maximum release of 99.81% at the end of 24 h [Figs. 9,10]. Formulation EF5 showed the slowest drug release and showed maximum drug release of 95.6% after 24 h. We could not detect any relationship between the drug release profile and the polymer composition. We can only conclude that the release mechanism might include diffusion as well as erosion since the biopolymer isolated is slightly soluble in water. The release data of tested strips were analyzed on the basis of the Korsmeyer–Peppas equation and Higuchi kinetics (by BIT-SOFT 1.12: drug release kinetics with model fitting). Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. The R^2 values for the Higuchi and Peppas kinetic models were calculated and compared. All the tested formulations gave good fit to the Korsmeyer–Peppas model. All formulations showed non-Fickian drug release (0.5<n<1). On the basis of above determinations, EF3 was selected as the best formulations.

In vitro permeation study is predictive of an *in vivo* performance of drug. This study was carried out using different formulations in a Franz diffusion cell using eggshell membrane. This study helps in confirmation of better permeation of drug through skin. Mean cumulative amounts of drug released per cm^2 of patch after 24 h were found to be 150.5, 389.9, 768.5, 512.2, 448.2, 309.1, 218.3, and 734.2 µg/cm^2 [Fig. 11].

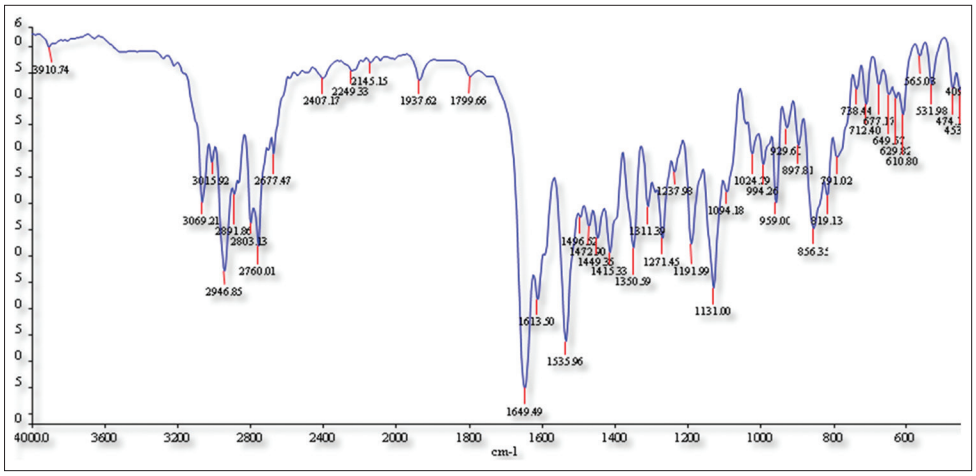

Fig. 6: Infrared spectra of drug risperidone

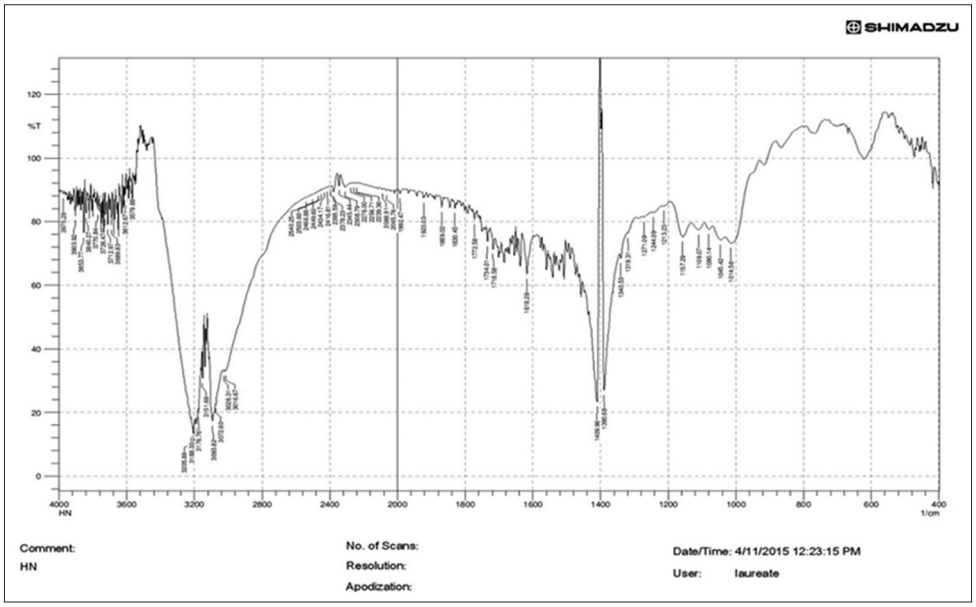

Fig. 7: Infrared spectra of *Euryale ferox* biopolymer

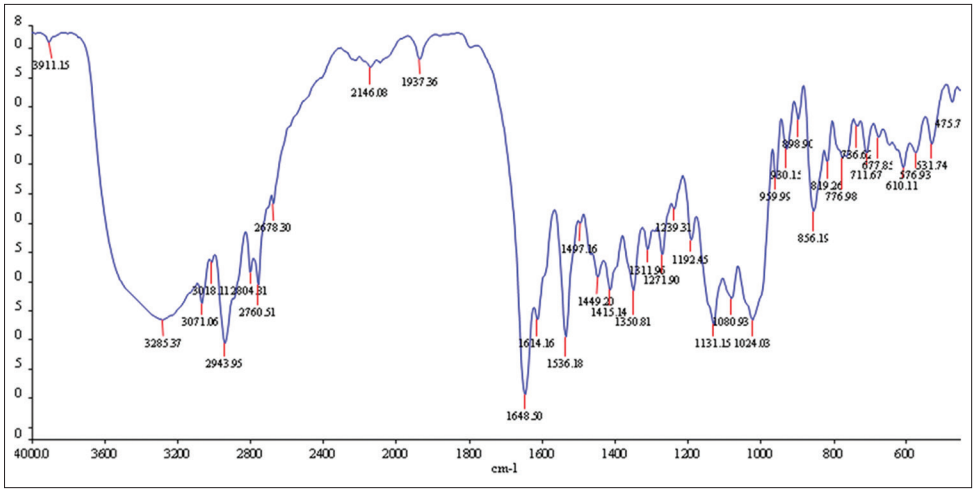

Fig. 8: Infrared spectra of drug, *Euryale ferox*

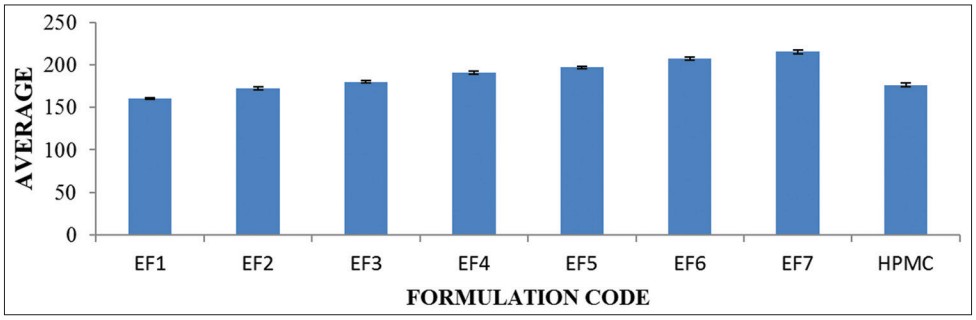

Fig. 9: Uniformity of weight of prepared bioflexi films using a different ratio of *Euryale ferox* mean (n = 3) ± standard deviation

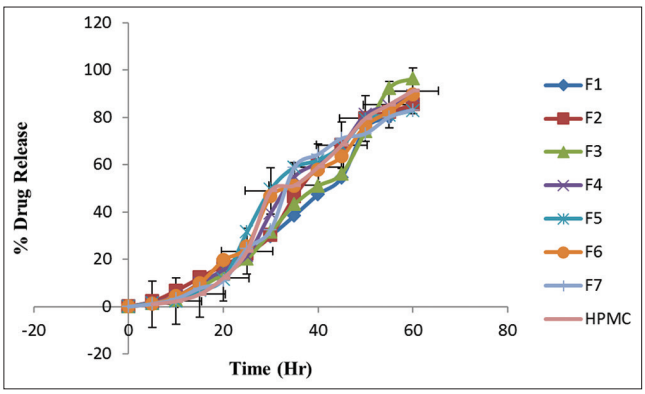

Fig. 10: Release profile of risperidone containing different concentrations of *Euryale ferox* mean (*n* = 3) ± standard deviation

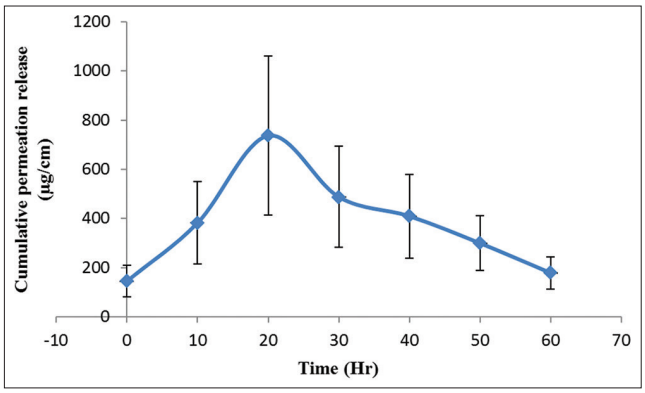

Fig. 11: *In vitro* permeation study of prepared bioflexi films from *Euryale ferox* mean (*n* = 3) ± standard deviation

CONCLUSION

Flexible, smooth, and transparent films were obtained. It was found that the bioflexi films EF3 showed best release and permeation. Again, it was concluded here that the formulation EF3 showed better permeability among the prepared bioflexi films for risperidone. Bioadhesive bio-lipstrip based on *E. ferox* biopolymer was developed and shown to release drug over the required period of time (12 h). Thus, a stable bio-lipstrip of risperidone for the treatment of psychosis using this novel biopolymer was demonstrated. The biopolymer showed good film-forming ability. Thus, this natural biopolymer could be promising excipient for the systemic delivery of drugs through labial route or other translabial routes.

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AUTHORS' CONTRIBUTIONS

Prof. Dr. N V Satheesh Madhav nucleated the project and implemented process methodology to be adapted during experimental work and also supervised and reviewed in preparation of manuscript. The experimental work development, optimization of the formulation, interpretation of results, and writing of this manuscript were done by Miss Bhavana Singh.

All authors read and approve the final manuscript.

COMPETING INTERESTS

The authors declare no conflicts of interest.

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