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Original Research Article

A smart spproach for delivering of nanosized olanzapine using piper betel biopolymer rate controlling flexi films for transvermillion delivery

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ABSTRACT

The aim of the study was to prepare and characterize the nanosize drug loaded bio-flexi films using the novel bioexcipient isolated from the fresh leaves of the *piper betle* (bioexcipient P) and to explore the potentiality of the lip skin as a novel transvermillion drug delivery system. The bioexcipient prepared using a simplified economical process and was subjected to various physiochemical evaluations along with the spectral analysis including UV, FT-IR, SEM, Mass and ^{1}H NMR. The nanosized bioflexi film formulated with the novel bioexcipient was screened for its functional properties, such as including filmability. Nanosized olanzapine loaded bioflexi films were formulated by using bioexcipient P as a film former and dextrose as a flexicizer. The formulated nanosized bioflexi films were subjected to various tests such as evaluating the, thickness, folding endurance, swelling index and in vitro release. The size of the nanoparticle was found to be 100 nm. The release of the nanosized olanzapine was maintained over 48 h, which was confirmed in *in vitro* release experiment. The results revealed that this biopolymer had a promising filmability and bioadhesivity. The formulated nanosized bioflexi films are feasible for delivering the olanzapine by transvermillion administration and for drugs that undergo first-pass metabolism.

Graphical Abstract

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Introduction

The skin of lip is exclusive and consists of primarily of tissue layer that has fewer and completely different glands compared with the normal skin. The lip is also in contrast to the alternative skin therein the outer layer (stratum corneum) is extraordinarily skinny or utterly absent in the general public. The translabial application of the medicine give many advantages, together with the shunning of viscus first-pass metabolism and skill to supply nearly constant drug delivery over a protracted amount, which can cut back general adverse effects. The skin forms a superb barrier against the drug permeation because of the rigid lamellar structure of the stratum lipids. Our novel translabial drug delivery sidesteps this barrier because of the terribly skinny or absent layer of stratum corneum [1–4].

Nanoparticles are investigated for several pharmaceutical functions due to their ability to guard drug from protein degradation, management the discharge of medicine, and enhance drug penetration and absorption at the particular membrane sites resulting in exaggerated bioavailability. Conjointly nanoparticle will offers a powerful adhesion attributable to the exaggerated contact space for van der Waals attraction [5–7]. Olanzapine, a BCS category II compound poorly soluble, however extremely permeable, exhibiting bioavailability that is restricted by the dissolution rate [8].

Olanzapine, a thienobenzodiazepine spinoff, belongs to the drug category called atypical antipsychotics, the newer generation of antipsychotics. Olanzapine works by block, or antagonizing, the Intropin D2 receptor. It is significantly appropriate for mental illness patients United Nations agency area unit initial eposide or treatment resistant psychosis [9, 10]. Additionally, olanzapine isn't related to a risk of blood disorder as seen with neuroleptic agent or clinically vital hyperprolactinaemia as seen with risperidone or prolongation of the QT interval. The drug includes a log P value of two that contributes to its lipoid solubility and hydrophilicity [11]. Recently, it was reported that, the sustained delivery of the olanzapine through a percutaneous route can avoid the toxicity due to the abrupt high blood concentration [12]. This study was undertaken to screen the potential of olanzapine for the translabial delivery.

Natural polysaccharides from biomaterial are widely used as bioadhesive materials due to their appropriate biocompatibility and biodegradability. The *Piper betle* biomaterial (biomaterial P) employed in this study was isolated from the leaves of *Piper Betle* that belongs to the family of *Piperaceae* [13]. The leaves contain carbohydrates, dietary fibre, fat, super molecules, and minerals. In our study, biomaterial P was used as a bioadhesive and film forming agent within the dosage form.

The aim of our research study was to isolate the biomaterial P, formulate nanosized drug loaded bioflexi films a combination of two potential approaches (mucoadhesive films and nanoparticle carriers) in one delivery system to improve dispersion of olanzapine, which undergo first-pass metabolism and to overcome the side effects which are encountered orally for effective patient compliance in psychotic patients.

Experimental

Materials and methods

Olanzapine (assigned purity, 99.8%) was provided by the Lifecare neuro Private Limited (Baddi, Himachal Pradesh, India). The piper betel leaves were purchased from the market of Dehradun, Uttarakhand, India. Sodium carboxy methylcellulose (CMC-Na) and sodium alginate

were purchased from Merck Specialities Private Limited (Mumbai, India). All other chemicals and solvents were of analytical grade.

Isolation of biomaterial P

Piper betel leaves were collected from the local market. *Piper betel* leaves paste (100 g) was treated with 500 mL of doubly distilled water and stirred with a mechanical stirrer at 4000 rpm for 1 h. The mixture was centrifuged at 4000 rpm for 30 min. The supernatant was treated with a triple volume of acetone and the mixture was refrigerated for 12 h, after which the mixture was centrifuged at 5000 rpm for 30 min. The supernatant was discarded and the insoluble material was dried in a vacuum desiccator for 14 h. The dried bioexcipient was purified by the hot dialysis method for complete removal of impurities like chlorides and sulphates. The procedure was optimized by repeating the procedure 6 times and the percentage yield was calculated. The purified bioexcipient P was screened through 200# mesh and stored in a desiccator for later use.

Preparation of olanzapine nanoparticles

Olanzapine nanoparticles were prepared by modified solvent evaporation method [15]. Solution of drug (specified amount) and methanol was prepared and sonicated for 5 cycles (3 min/cycle in ultrasonic bath sonicator). Till the solution become turbid and then sonicated again. The resulting solution was then centrifuged at 3000 rpm for 20 min. The nanoparticles obtained were collected and washed with distilled water and dried at room temperature.

Preparation of bioadhesive bio-flexi films

Bioexcipient P (100 mg) was placed in a mortar and 80 mg of dextrose was added. Both were triturated for 15 min, after which 10 mg of the nanosize olanzapine was incorporated in a geometrical dilution pattern. Doubly-distilled water (10 mL) was added dropwise with constant trituration. The mixture was subjected to magnetic stirring for 30 min and sonicated at 400 Hz for 5 cycles of 60 s each in order to obtain a colloidal mixture. The colloidal mixture was poured into a culture dish with a diameter of 6 cm and was evaporated at room temperature for 12 h, allowing a dried film to form. The film was carefully removed and cut into 2 cm x 2 cm squares. A similar procedure was adopted for other concentrations of the bioexcipient P, HPMC and pectin polymers (Table 1).

Physicochemical characterization of olanzapine nanoparticles

The zeta potential, particle size and the size distribution of the olanzapine nanoparticle was measured using Malvern zeta sizer 2000, UK. The surface charge determination was performed using an aqueous dip cell in an automatic mode by placing diluted samples in the capillary measurement cell and cell position was adjusted.

Characterization of biomaterial P

The isolated bioexcipient P was subjected to physicochemical analysis, including solubility, colour changing point, colour, texture, protein and carbohydrate content, SEM analysis, FT-IR and DSC, mass spectrometry and ^{1}H NMR spectroscopy studies.

It was further evaluated for its adhesiveness using a shear stress method and a rotating cylinder method. The results were compared with the commonly used adhesive material, CMC-Na.

In vitro adhesive study using shear stress method

Mucoadhesive properties of the bioexcipient P was determined in vitro using the shear stress method. Three different concentrations of the bioexcipient P (1%, 3% and 5%) were placed between two glass plates and subjected to a shear stress for assessment for *in vitro* adhesive strength in terms of weight required for breaking adhesive bonds between the material and the glass plate after a specified contact time of 5, 10, 15 and 30 min. The results were compared with the polymer CMC-Na (1%) [16].

Rotating cylinder method

The adhesion time of the bioexcipient P was compressed on a disc to goat intestinal membrane was evaluated by the rotating cylinder method using a USP Type-II dissolution apparatus. Freshly cut intestinal membrane was attached to the cylindrical basket. The compressed disc was carefully adhered to the membrane by prior wetting with water. The cylinders were positioned in the basket containing 900 mL of phosphate buffer at pH 7.4 at 37 ± 2°C. The study was conducted at a speed of 100 rpm. The disc was observed at different time intervals. The time required for dislodgement of the disc was recorded and the study was conducted in triplicates. The results were compared with the standard polymers such as CMC-Na and sodium alginate [17].

Table 1. Formulation of various bioflexi films

Serial no.	Ingredient	SA1	SA2	PB1	PB2	PB3	PB4	PB5	PB6
1	Olanzapine (mg)	10	10	10	10	10	10	10	10
2	Piper betel (P.) biopolymer (mg)	-	-	100	200	300	400	500	600
3	Sodium carboxy methyl cellulose (mg)	400	-	-	-	-	-	-	-
4	Sodium alginate (mg)	-	400	-	-	-	-	-	-
5	Dextrose (mg)	110	110	110	110	110	110	110	110
6	Distilled water (mL)	10	10	10	10	10	10	10	10

Drug- excipient interaction study

The pure drug along with formulation excipients was subjected to interaction studies.

UV spectroscopy

The study was carried out by dry and wet mixing of drug and excipients in the ratios of 1:1, 1:3, 1:5, 3:1, and 5:1. Both types of mixtures were stored at room temperature and at 55°C for five days. The appropriate dilutions were done with methanol and pH 7.4 phosphate buffer and the samples were scanned at λ_{max} using the UV spectroscopy.

Colourimetery

The study was carried out using various reagents including potassium permanganate, crystal violet, iodine, copper sulphate, potassium dichromate, methyl red, methyl orange and ferrous sulphate were incorporated on different section of glass plate. The pure drug and drug along with biopolymer P was subjected to colourimetery for drug-excipient interaction study.

Characterization of drug-loaded bio-flexy films

Thickness

The thickness of five randomly selected bio-flexy films was evaluated at five different corners (the four corners and the centre) on a single patch of each formulation using a screw gauge and mean value was calculated [18].

Weight uniformity study

Five bio-flexy films with the surface area of 1 cm^2 were randomly selected from each formulation. Each strip was weighed and the study was performed in triplicate and average weights were calculated [18, 19].

Content uniformity

Formulated drug loaded bio-flexy films were evaluated for uniformity the of drug content. Strips of 1 cm^2 from each formulation were randomly selected and transferred into a 100 mL volumetric flask containing a mixture of pH 7.4 phosphate buffer and methanol. The flask was stirred for 4 h on magnetic stirrer. A blank control was similarly prepared using the drug free bio-flexy film. The obtained solutions were filtered through a 0.45 µm membrane. The drug content was then evaluated after proper dilution using UV spectrophotometry [20].

Folding endurance

Folding endurance for all drug loaded bio-flexy films was calculated by using a film with area of 4 cm^2 from each formulation. The selected bio-flexy films were subjected to folding endurance by repeatedly folding at the same place till its break down. The number of folding required to break or crack a strip was recorded as folding endurance. The measurement was repeated in triplicate [20, 21].

Swelling index

Drug loaded bio-flexy films with a size of 1 cm^2 from each formulation were selected for swelling study. Each bio-flexy film was placed on a cover slip and placed in culture dish and 10 mL of phosphate buffer was added. After 1 h the cover slip with bio-flexy film was weighed. The difference in weights gives the weight increase due to absorption of water and swelling of bio-flexy film [22]. The procedure was repeated three times to get concordant values and the swelling index (S) was determined by equation (Equation-1).

$$S(\%) = (Xt - Xo) \times 100\% \quad (1)$$

Where X_t is the weight of swollen bio-flexy film after time t and X_o is original weight of bio-flexy film.

Percentage moisture absorption (PMA)

Percentage moisture absorption study for all formulated bio-flexy films was determined using 1 cm^2 of drug loaded bio-flexy films. The bio-flexy films were transferred in a watch glass and placed in a desiccator containing saturated solution of aluminium chloride for 72 h. The weight gain by the film was calculated [23]. The study was performed three times and the percentage moisture loss was calculated by using the formula:

Moisture absorption (%)
= [(final weight – initial weight) / initial weight] × 100% (2)

Flatness

Longitudinal strips were cut from the prepared drug loaded bio-flexy films and the length of each strip were measured and then difference in the lengths due to the non-uniformity I flatness was measured. Flatness was calculated by measuring narrowing of strips and a zero percent constriction was

considered to be equal to a hundred percent flatness [24].

$$\text{Constriction (\%)} = (l_1 - l_2)/l_1 \times 100 \quad (3)$$

Where, l_1 initial length of each strip; l_2 final length

Surface pH study

The surface pH of the drug loaded bio-flexy films was determined using a glass electrode. The bio-flexy films were allowed to swell by keeping them in contact with distilled water for 1 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the bio-flexy films and allowing it to become constant for 1 min. The experiments were performed in triplicate and average value was noted [25].

Water vapour transmission test (WVT)

WVT is defined as the amount of moisture transmitted through a unit area of strip in unit time. A glass bottle filled with 2g anhydrous calcium chloride and adhesive spread across its rim was used in study. The bio-flexy film was fixed over the adhesive and the assembly was placed in a sealed desiccator containing 200 mL of saturated potassium chloride solution. The weighed bottle was then placed in the desiccator and the procedure was repeated [26].

$$\text{WVT} = W/ST \quad (4)$$

Where W is the increase in weight in 24 h, S is area of strip exposed (cm^2), and T is the exposure time.

In-vitro diffusion

The *in-vitro* drug diffusion assay was carried out in the M.S. diffusion apparatus. This was static method and requires complete replacement of the sample. Dialysis membrane was tied to the terminal portion of the cylindrical donor compartment. A 1 cm^2 bio-flexi film was kept above the dialysis membrane in the donor compartment, and the receiver compartment was filled with diffusion medium. The complete sample was withdrawn at different time intervals and the receiver compartment was refilled with fresh medium. The amount of the drug released was assessed by measuring the absorbance at 247 nm using the UV spectrophotometer [27].

Stability studies

Optimized bio-flexy films were subjected to stability study. Bio-flexi films were wrapped in aluminium foil. These films were kept in stability chamber and maintained at 37 ± 5 °C and 75 ± 5% RH for 6 month. The changes in appearance, physical characteristics and release behaviour of the stored bio-flexi films were investigated after 1-6 months. The data presented are the mean of three determinants [28].

Results and Discussion

Physicochemical properties of olanzapine nanoparticles (zeta potential and particle size)

The particle size of olanzapine was analysed by zetasizer. The z-particle size of nanoparticles ranged from 110 nm to 152.7 nm. The ability of nanoparticles to alter the biodistribution and pharmacokinetics of drug has important *in vivo* therapeutic application. So, the size and surface characteristics of nanoparticles are of prime important. Nanoparticles ranging 150 nm are easily captured by Kupffer cells or other phagocytic cell population that restrict biodistribution. These systems help in prolonging the duration of drug activity and increase the targeting efficiencies to specific site. Particle size distribution graph for formulation (PB2) is shown in Figure 1. The electric charge present on the nanoparticles was evaluated by

measuring the zeta potential as revealed in Figure 2. The zeta potential of the all formulated nanoparticles was in the range of -2.65 to -19.2 mV which indicates moderate stability with no agglomeration.

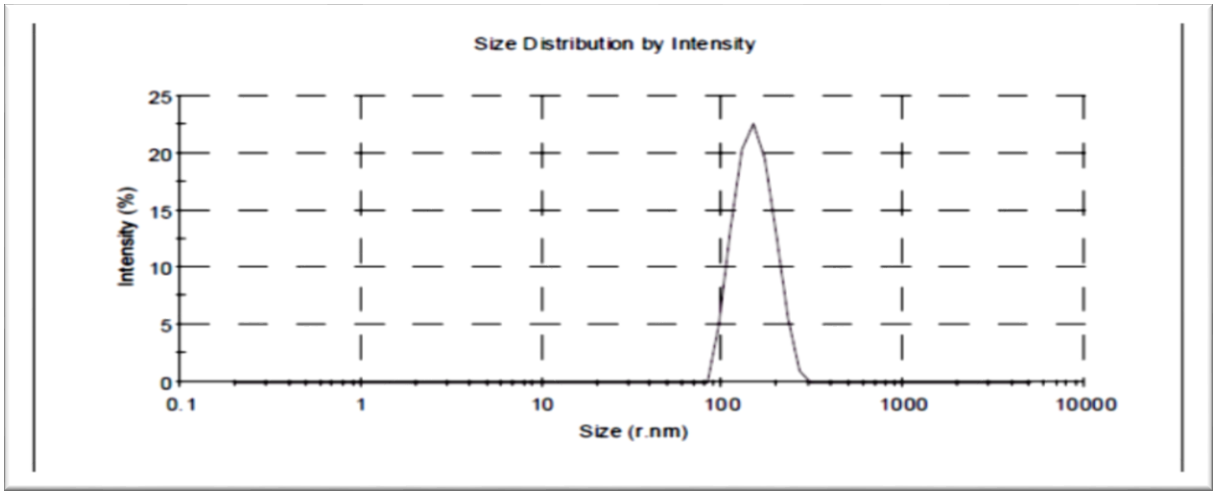

Figure 1. Particle size distribution curve of nanosize olanzapine

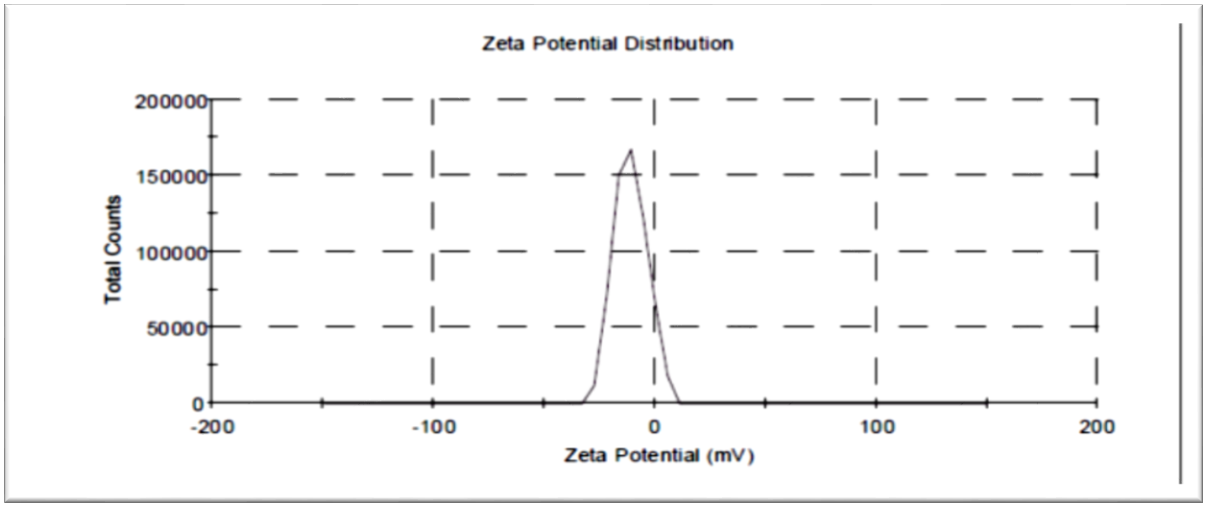

Figure 2. Zeta potential curve for nanosize olanzapine

Spectral analysis of biomaterial p

The isolated biomaterial P was smooth, amorphous, brownish, and slightly soluble in water. The yield was found to be 2.00 ±0.005% w/w. The biomaterial P showed a positive test for Fehling's solution and a positive ninhydrin test, which revealed the presence of carbohydrate and protein, respectively. The λ_{max} for biomaterial P was found to be 282 nm and the melting point was found to be 260 °C respectively. The IR spectra revealed the

presence of carboxylic acid (3159.40 cm^{-1}), alkenes (3126.61 cm^{-1}), aromatics (3014.74 cm^{-1}), hydroxyl group (2585.21 cm^{-1}) and esters (1772.58 cm^{-1}) (Figure 3). These functional groups including, ketonic and nitro group are responsible for adhesion activity of the biopolymer as these same groups are observed in mucoadhesive polymer like HPMC and polycarbophill. The NMR spectra showed delta value at 2.49, 3.68, and 8.14 which reveal the presence of hydroxyl, ester and aromatic groups respectively (Figure 4). The mass spectrum showed large molecular weight structure likely to be polymeric and presence of proteins. It showed a parent peak at m/z 1151.51 (Figure 5).

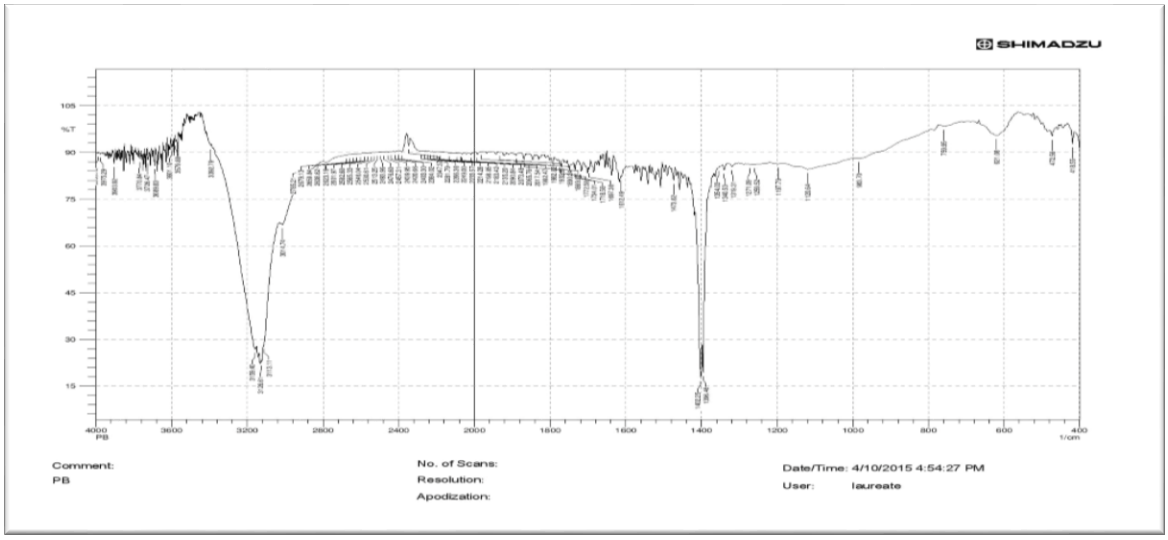

Figure 3. IR spectrum of isolated biopolymer P

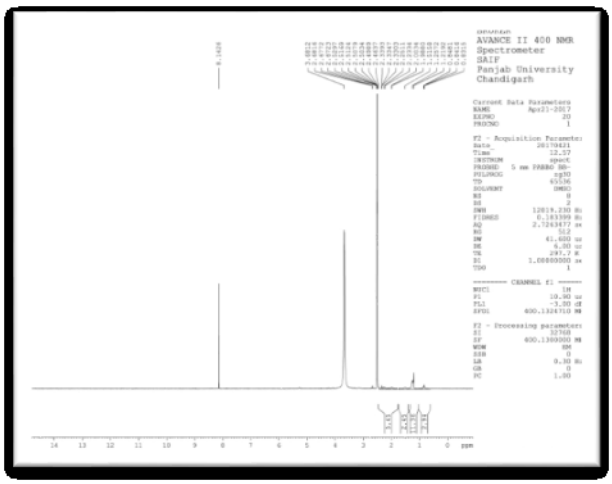

Figure 4. NMR sp ectra of isolated biopolymer P

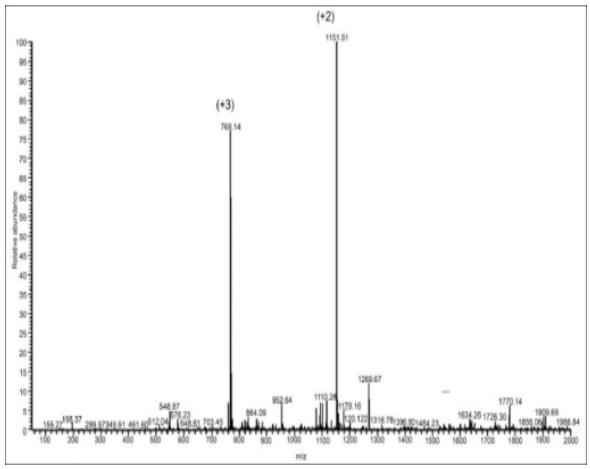

Figure 5. Mass spectrum of isolated biopolymer P

SEM of biomaterial P

The surface arrangement of the biomaterial P revealed that it has rough, flakes like structure

with additional granular structure on the flaky surface. This clearly indicates it is granular and polymeric in nature (Figure 6).

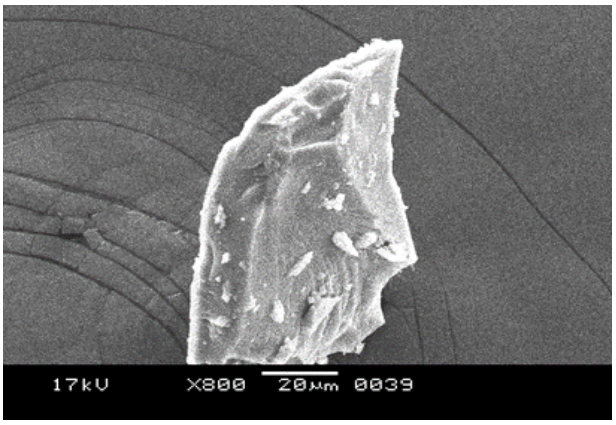

Figure 6. SEM image of the isolated biomaterial P

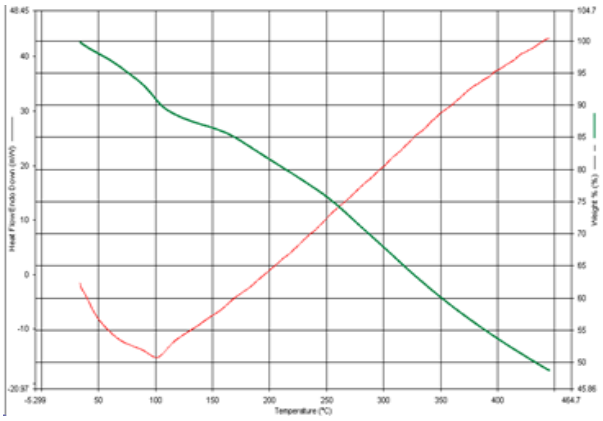

Figure 7. Result of the DSC analysis of the isolated biomaterial P

Adhesivity of biopolymer P

The results of the adhesion tests showed that the biomaterial P had a significant adhesion in comparison with the HPMC and Na-CMC. The result of the adhesion test revealed that the isolated biomaterial P from the leaves of piper betel possesses notable bio/muco adhesivity.

Drug-excipient interaction study

The drug interaction study revealed that there was no interaction between the drug and the excipients, including the biomaterial P, because there was no change in the λ_{max} value, 282 nm.

In the colourimetery interaction study olanzapine showed colour change with potassium permanganate from pink to brown which indicate the reaction of the potassium permanganate due to saturation of the double bonds. Drug and biopolymer P (1:1) ratio also showed same colour change with potassium permanganate. This revealed that drug was not entrapped. After performing UV method the λ_{max} of drug-biopolymer P was found near to pure drug. This showed there was no interaction between drug and biopolymer P. So, it was found that the biomaterial was useful in formulation of the bioflexi films. The drug-biopolymer P showed no colour change with other reagents, as well.

Thickness, swelling index, surface ph and folding endurance

The average thickness of the all prepared bio-flexi films ranged 0.39 ± 0.05 to 0.50 ± 0.08 mm. Weight variation values of all films (1 cm^2) were found in the range 30.75 ± 0.30 to 42.95 ± 0.37 mg. Thus, the equivalent gain in the weight of the films was observed as the thickness of films increased. The values were uniform for the films within each formulation type, indicating that the film casting was uniform.

The range of the swelling index for the bioflexi films was found to be 105.33 ± 0.58 to 157.65 ± 0.68. The swelling index suggests that they will cause minimum discomfort when in

use. This property of the film had significant influence on the release of the drug.

The surface pH for all the formulations was found to be ranging from 6.32 ± 0.30 to 6.52 ± 0.42. Due to the fact that pH range of the film was close to the skin pH, no skin irritation was expected.

The folding endurance of the films was at the range of 115 ± 0.50 - 190 ± 0.45. High folding endurance values for films indicate high mechanical strength. This is highly required because it would prevent dislocation of the film from the site of application or breaking of the film while applying it.

Skin irritation, moisture absorption, flatness, wvt and content uniformity

In the all formulations, no skin irritation, redness or erythema was observed during the primary skin irritation. The moisture uptake of bioflexi films ranged from 3.00 ± 0.20% to 5.00 ± 0.39%. The moisture uptake of the formulation was low, which protects the formulation from microbial contamination and reduces bulkiness. The range of WVT for the bioflexi films was found to be 5.00 ± 0.41 to 7.50 ± 0.50. The range of content uniformity for the bioflexi films was found to be between 90.58 ± 0.79% to 95.00 ± 0.75%. There was no significant difference in the drug content among all the bioflexi films, indicating a uniform dispersion of the drug throughout the films.

In vitro release

The in vitro release of olanzapine for the different films is shown in Figure. All the formulations released > 90% of the drug within 10 h. Formulation PB2 showed maximum release of 95.81 % at the end of 48 h. Formulation PB4 showed the slowest drug release of 90.12% after 12 h. The only inference is that the release mechanism might include diffusion as well as erosion, since the biopolymer was slightly soluble in water. The release data of bioflexi films was analysed on the basis of the Krosmeyer-Peppas equation and Higuchi kinetics (by BIT-SOFTWARE). Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. The R^2 value for the Higuchi and Peppas kinetic models were calculated and compared. All the tested formulation gave good fit to the Krosmeyer-Peppas model. All formulations showed non-Fickian drug release ($0.5< N <1$). On the basis of above determination, PB2 was selected as the best formulation.

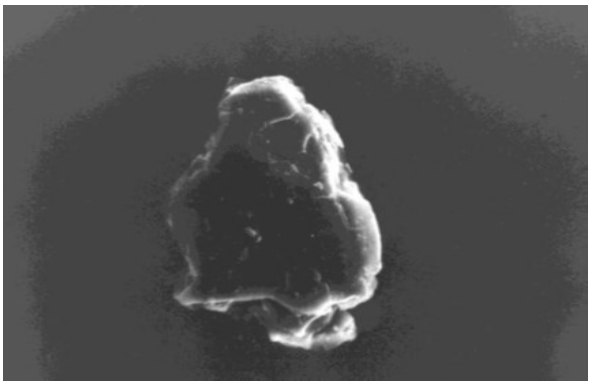

Figure 8a. SEM image of Olanzapine drug molecule film after present in the bioflexi film

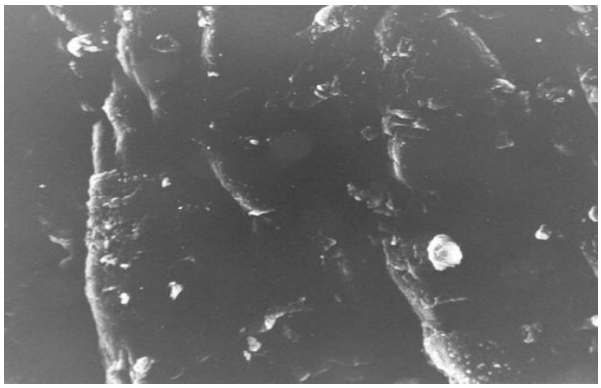

Figure 8b. SEM image of Bioflexi film after drug release

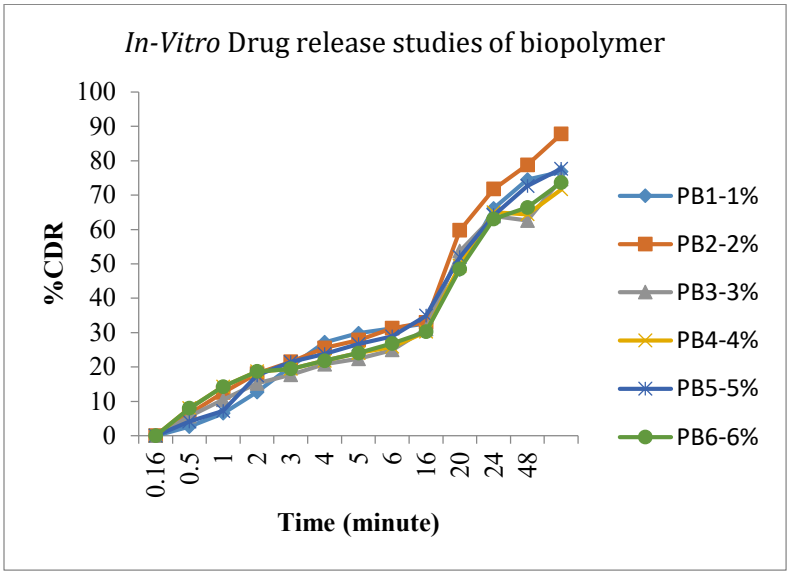

Figure 9. *In-vitro* release of olanzapine from bioflexi films with different concentration of biopolymer P (1-6%)

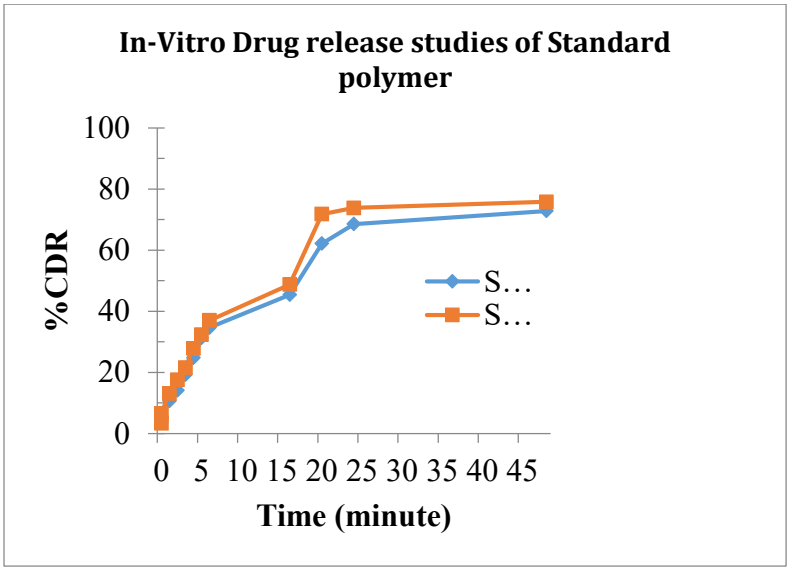

Figure 10. *In-vitro* release of olanzapine from bioflexi films of CMC-Na (4%) and Sodium alginate (4%)

Stability studies

At the end of the stability study, the formulated bioflexi films demonstrated almost no drug loss. The bioflexi films also showed an insignificant difference in the *in vitro* drug release. All optimized the film revealed satisfactory flexibility and elastic properties during and at the end of the accelerated stability period. This indicated that there was no influence on the chemical and physical stability of the formulation during the test period.

Conclusions

In the present study, the bioflexi films based on the piper betel biopolymer were developed and analysed for the drug release over the required period of time (48 h). Biopolymer isolated from leaves of piper betel used in preparation of nanosize olanzapine loaded bioflexi films which act as an efficient carrier for delivery of olanzapine at a controlled rate. It may significantly improve the ability to cross blood-brain barrier and act as an effective tool to treat psychosis. Also, this natural biopolymer is capable of serving as a promising excipient for the systemic delivery of drugs through the translabial route or other transdermal route.

Acknowledgement

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Disclosure statement

No potential conflict of interest was reported by the authors.

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