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MUCOADHESIVE BIO-FLEXY FILM OF *PHOENIX DACTYLIFERA* LOADED WITH PHENYTOIN FOR TRANSLABIAL DRUG DELIVERY

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Keywords:

Phoenix dactylifera, Phenytoin, Translabial, Mucoadhesive, Bio-flexy film

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ABSTRACT: Translabial drug delivery system is an attractive approach for drug delivery system possess advantages as a bypass of the first-pass metabolism, prevent from digestive enzymes and rapid action of suitable drugs. The purpose of the current research work is to isolate the biopolymer from *Phoenix dactylifera* (date palm) and prepare mucoadhesive bio-flexy films loaded with Phenytoin. The isolated biopolymer was subjected to various physicochemical characterization procedures for analyzing the mucoadhesive and mucoretentive properties. The mucoadhesive and mucoretentive properties of isolated biopolymer were analyzed using the shear stress method and the MS mucoretentibility method. The formulated Phenytoin loaded bio-flexy films were evaluated for weight, thickness, folding endurance, swelling index, surface pH, tensile strength, *etc*. The *in-vitro* drug release studies were analyzed using the static MS diffusion apparatus. Phenytoin loaded with HPMC and sodium CMC was used as standard film, and then results were compared. The optimized bio-flexy films shows order PD6 > PD5 > PD4 > PD3 > PD2 > PD1 on the basis of percentage release. The percent release of optimized formulation (PD6) bio-flexy film was 97.1±2.08%. The C_{max}, $T_{max,}$ and AUC for PD6 bio-flexy films were found out to be 9.80 µg/ml, 8 h, and 154.85 µg h /ml, respectively. Stability studies were performed for the optimized bio-flexy films as per ICH guidelines. The resultant bio-flexy film formulation possesses an improved drug release with good mucoadhesivity and stability. Thus, the bio-flexy film of *Phoenix dactylifera*, shows potential for a translabial drug delivery system.

INTRODUCTION: Phenytoin is found in 1940 and became a first-line anti-epileptic drug mainly prescribed in the treatment of seizures by decreasing abnormal electrical activity in the brain and also slowing down impulses in the brain [1]. The key advantage of Phenytoin is the capability to prevent status and grand mal seizures without causing drowsiness like the majority of other anti-epileptic drugs [1]. The mechanism of action of Phenytoin is that it works by blocking the voltage-sensitive channels in the neurons. It decreases the potential of the neuron to fire action potential [2].

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The oral dose of phenytoin reported hypersensitive allergic reactions like itching, rashes, *etc*. with hematologic side effects as megoblastic anemia. Phenytoin causes slight abnormalities in newborns like craniofacial anomalies and mental retardation. It reported suicidal tendency when given a prolonged period of time [2-4]. Thus to eliminate the severe side effects of the drug when given orally for a prolonged period of time, novel drug delivery of translabial dosage form has been selected to target the drug at the specific site of action. In the transtibial drug delivery system, the absorption of the drug occurs *via* the mucosal membrane of the lips. This system has distinct advantages: high patient acceptability, quick onset of action both locally and systematically due to the rich blood supply, greater bioavailability or improved therapeutic efficacy, more uniform plasma level, less chances of toxicity, and longer duration of action [5].

Thus the use of mucoadhesive bio-flexy films for translabial drug delivery can reduce the dose and severe side effects of Phenytoin.

The biopolymer was isolated from *Phoenix dactylifera* (Date Palm), which belongs to the family of Arecaceae [6]. The biopolymer (*Phoenix dactylifera*) that is isolated from a natural edible source is economical and safe to use. *Phoenix dactylifera* have medicinal properties for colds, fever, cystitis, edema, throat infection, abdominal trouble *etc*. They have an excellent nutrient profile and high antioxidant properties, which may help variety of health benefits. Pulp and seeds of *Phoenix dactylifera* contain oil and fatty acid. It contains a high amount of oleic acid, minerals like cobalt, nickel, *etc*., amino acids, and tannins [7]. In the present research work, we focused on the formulation of mucoadhesive bio-flexy films of *Phoenix dactylifera* loaded with phenytoin.

MATERIALS AND METHODS: Phenytoin drug was obtained as a gift sample from Zaneka Pharmaceuticals., Haridwar. *Phoenix dactylifera* was procured from the local market, Dehradun. HPMC and sodium CMC were purchased from Merck Specialties Pvt. Ltd.; Mumbai. Other ingredients and double distilled water are of analytical grade.

Isolation of Biopolymer: Method for isolation of biopolymer from the pulp of *Phoenix dactylifera* showed in **Fig. 1.**

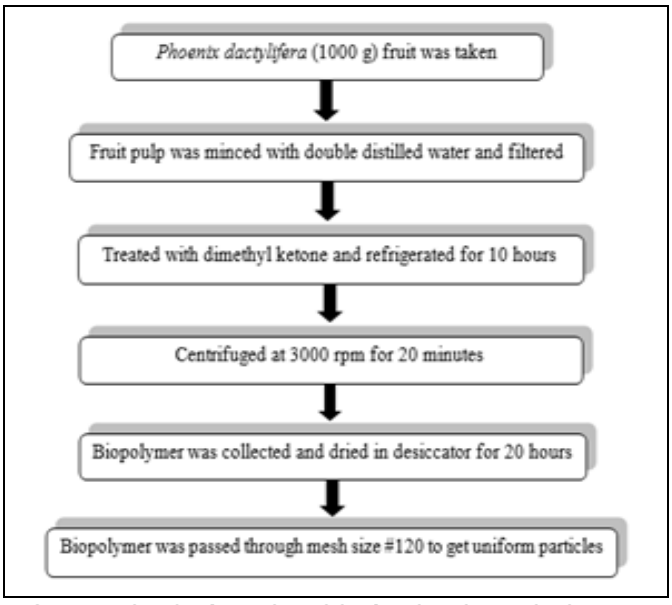

FIG. 1: FLOWCHART OF ISOLATION OF BIOPOLYMER OF *PHOENIX DACTYLIFERA*

Physico-Chemical Characterization of Isolated Biopolymer: The isolated biopolymer was characterized by various physicochemical parameters like its color, odor, solubility, color-changing point and certain chemical tests [8] like Molisch's test and Fehling reagent (Carbohydrates), [9] Biuret test (Proteins) and starch [10]. The Melting point of the extracted biopolymer was checked by using melting point apparatus, color was inspected by visual check, and the solubility was analyzed by dissolving the biopolymer in various solvents.

Phoenix dactylifera isolated biopolymer was subjected for various spectral analyses using IR spectroscopy, 1H NMR spectroscopy, MS (Mass spectroscopy), DSC (differential scanning calorimetry). The results obtained from spectroscopy analysis were subjected for interpretation, and the results were inferred [11, 12].

SEM for Surface Morphology of Isolated Polymer: The surface topology of the biopolymer was studied by a Scanning electron microscope (SEM). This instrument produces signals through which surface topography, composition, morphological examination of the surface, and internal structure of the sample can be determined. SEM is also used for the elemental analysis of the biopolymer to give details of elemental composition [11, 12.]

Mucoadhesive Property of Isolated Polymer: The isolated biopolymer was subjected to mucoadhesive property, and mucoadhesive was determined with the shear stress method. Firstly isolated biopolymeric solution was prepared using distilled water as a solvent in various concentrations ranging from 1-5% w/v. Each solution was used for determining *in-vitro* bond-breaking strength or force required to break the bond at several contact intervals (5, 10, 15, 20, 25, and 30 min). A similar procedure was followed for standard polymers Sodium CMC and HPMC [13, 14.]

Mucoretentive Property of Isolated Polymer: Mucoretaintability was determined by M.S. Mucoretaintability method using an animal model of goat mucosa, *i.e.*, *Capra aegagrus* labium as mucosal substrate using a thin film of biopolymer with phosphate buffer pH 6.5. The dislodgement time of bio-flexy film from the mucosal substrate

was reported at fixed time intervals, and obtained data was compared with a standard film of Sodium CMC and HPMC polymer [14].

Acute Toxicity Studies: According to the OECD guidelines, the study of the single-dose acute study was performed on rats for 2 weeks (wistar rats, either sex, 200-250 g). The protocol for the study was approved by the Institutional Animal Ethical Committee (Registration number 1156/AC/07/ CPCSEA). The solution of the biopolymer was prepared according to the bodyweight of the rat, *i.e.*, 5g/kg. The polymer solution was administered orally to the rat, and changes in physical changes were observed as body weight, itching, lacrimation, swelling, inflammation, redness, *etc*. If no changes were observed in the rat during the study, then biopolymer was found to be non-toxic and can be used for further study *i.e.*, for the preparation of biofilms of phenytoin [15, 16].

Preparation of Standard Curve of Phenytoin: The standard curve was prepared as per IP (Indian Pharmacopoeia, 1996) in various solvents for labial with pH 6.5, phosphate buffer with pH 7.4, and methanol at a concentration range from 1-10 µg/ml. Absorbance was determined using UV/Visible spectrophotometer, and the standard curve of phenytoin was plotted between the concentration (µg/ml) and absorbance. R^2 value and y-intercept were determined from the curve.

Formulation of Drug Loaded Bio-Flexy Film: The preparation of bio-flexy films of phenytoin loaded drug was performed by solvent casting method [17] in these different ratios of isolated biopolymer from PD1-PD6 as given in **Table 1**. Firstly biopolymer of *Phoenix dactylifera* was dissolved in distilled water with mannitol and dextrose, which act as a plasticizer. The resulting mixture was poured into the Petri plates and finally dried at room temperature until bio-flexible films were formed. After drying, the bio-flexy films were scrapped out from the Petri plates and carefully checked for any imperfection, and then the bio-flexyfilm was cut into the size of 1 sq. cm, by using fabricated punch [18, 19].

TABLE 1: FORMULATION OF PHENYTOIN LOADED BIO-FLEXY FILM FROM *PHOENIX DACTYLIFERA* (PD) BIOPOLYMER

Ingredients	PD1	PD2	PD3	PD4	PD5	PD6	HPMC film	Sod CMC film
Phenytoin (mg)	100	100	100	100	100	100	100	100
Phoenix dactylifera (mg)	50	100	200	300	400	500	-	-
HPMC (mg)	-	-	-	-	-	-	300	-
Sodium CMC (mg)	-	-	-	-	-	-	-	300
Dextrose (mg)	100	100	100	100	100	100	100	100
Mannitol (mg)	100	100	100	100	100	100	100	100
Water (ml)	10	10	10	10	10	10	10	10

Evaluation of Drug Loaded Bio-Flexyfilms: The prepared bio-flexy films were subjected to various evaluation parameters like weight uniformity, thickness, folding endurance, physical appearance, swelling index, surface pH, tensile strength, percent elongation, percent moisture uptake, percent moisture loss, vapor transmission rate, and drug uniformity content.

Physical Appearance: The prepared bio-flexy films were checked visually according to the various parameters like texture, clarity, flexibility and smoothness in order to check the uniformity of prepared bio-flexyfilms. All prepared biofilms of *phoenix dactylifera* were found to be translucent, flexible, and smooth surface [20].

Weight Uniformity: Three prepared bio-flexy films were taken of 1 sq.cm and weighed by using weighing balance, and after that, the mean was calculated [21, 22]. The weight of various phenytoin-loaded bio-flexy films was found in the range of 41.77±0.61 to 82.45±0.02mg.

Thickness: The Thickness of formulated bio-flex films was determined by using a screw gauge and the thickness of phenytoin loaded bio-flexy films were found in the range of 0.46±0.01 to 0.73± 0.01mm.

Folding Endurance: The Folding endurance of formulated bio-flexy films was determined by continually folding the biofilm at the same place until it was broken. The number of times the bio-flexyfilm could be turned at the specific position without cracking was recorded [23]. The phenytoin-loaded bio-flexy films showed folding endurance from the range of 132.00±1.73 to 183.00±1.00 times.

Swelling Index: The swelling index of prepared bio-flexy films was determined by placing the bio-flexy films in the Petri plates having 10 ml of phosphate buffer pH 6.5. The swelling index (S %) was determined by using the following formula [21]:

$$S\% = \left(\frac{X_t - X_0}{X_0} \right) \times 100$$

Where,
X_t = Weight of swollen bio-flexy film after time t
X_0 = initial weight of bio-flexy film

The phenytoin-loaded biofilms showed a swelling index in the range of 28.46±1.70% to 38.73±1.41%.

Surface pH: The surface pH was calculated for the individual prepared bio-flexy film by, placing them in a petriplates with 0.5 ml of water kept it for 30 seconds. The prepared bio-flexy films surface took into contact with the electrode of the digital pH meter and surface pH was determined [21]. The prepared bio-flexy films loaded with phenytoin drug showed a pH in the range of 6.80±0.05 to 7.10±0.10. The measured surface pH for all batches was found close to the neutral pH, which clearly shows no risk of labial irritation or damage.

Tensile Strength: Tensile strength of the prepared bio-flexy films was determined by universal strength testing apparatus [17]. The prepared bio-flexy films of a specific size (1 sq.cm) were fixed between glass plates, and strings and weights are applied until the bio-flexy films breaks. The tensile strength of prepared bio-flexyfilm was directly measured from weight required and reported. The tensile strength of prepared bio-flexy films loaded with phenytoin was found in the range of 91.32±0.99 g to 142.44±0.21 g.

Percent Elongation: The prepared bio-flexy films were attached on one end to a vertical board and pulling it carefully on the other end until it breaks. The length at this breaking point was determined. The increase in length was determined and divided by the initial length of biopolymer [22]. The observed percent elongation of phenytoin-loaded prepared bio-flexy films was found in the range 7.95±0.45% to 10.39±0.17%.

Percent Moisture Uptake: The percentage moisture loss of formulated bio-flexy films was determined by 1 sq. cm of bio-flexy films from every formulation were weighed separately and keep in a desiccator which containing fused anhydrous calcium chloride for 48 h [14]. Each prepared bio-flexyfilm was again weighed after 48 hours, and the percent moisture uptake was calculated through the formula.

Percent moisture uptake = [(Final weight - initial weight / Initial weight)] × 100

The prepared bio-flexy films loaded with phenytoin showed a percent moisture uptake in the range 6.26±0.06% to 11.25±0.26%. The percent moisture uptake revealed that none of the phenytoin-loaded biofilm shows significant moisture absorption; this indicates that the bio-flexyfilm formulations were stable at high humid conditions.

Percent Moisture Loss: [23] The percent moisture loss was performed on the bio-flexy films was by taking three prepared biofilms of 1 sq.cm size. Then bio-flexy films were weighed and kept in a desiccator which containing fused anhydrous calcium chloride for 48 h. Finally, the weight loss of the bio-flexy films was determined using the following formula:

Percent moisture loss = [(Initial weight - Final weight / Initial weight)] × 100

The results revealed that bio-flexy films loaded with phenytoin showed a percent moisture loss in the range 6.85 ± 0.11% to 11.27 ± 0.23%. The physical integrity of phenytoin-loaded bio-flexy films was measured in terms of percent moisture loss which revealed the loss of water vapor from the bio-flexy films at dry conditions, and a conclusion was drawn that that if the formulation shows a higher degree of moisture loss, it becomes brittle and loses its flexibility.

Vapor Transmission Rate: This study was performed using a glass bottle with 5 cm length and internal diameter of 0.8 cm and filled with 2 gm anhydrous calcium chloride. The bio-flexyfilm was placed over the adhesive, and the assembly was kept and sealed in a desiccator containing 200 ml saturated solution of potassium chloride. The weighed bottle was then kept in a desiccator for 24 h and reweighed [23].

VTR was calculated using formula:

$$VTR = W/ST$$

Where,
W = Increase in weight in 24 hours
S = Area of strip exposed (cm^2)
T = Exposure time.

The bio-flexy films loaded with phenytoin showed a vapor transmission rate in the range 6.48±0.54 g/cm/h to 11.26±0.26 g/cm^2/h. This value of Vapor Transmission Rate (VTR) is optimal and essential for satisfactory drug release from the bio-flexyfilms.

Drug Content Uniformity: The bio-flexy films of 1sq. cm size from each prepared formulation was randomly selected and transferred into a volumetric flask (100ml) which containing 7 ml phosphate buffer (pH 6.5) and 1 ml methanol. The volumetric flask was stirred for 4 h on a magnetic stirrer. The achieved solutions were filtered through a 0.45µm membrane. The drug content was then determined after proper dilution using U.V Spectrophotometry through Shimadzu 1800 UV-Visible spectrophotometer [24]. The drug content found in the bio-flexyfilm varied from 90.63±0.52% to 97.28± 0.08%. The results of drug content uniformity showed that the phenytoin drug was uniformly dispersed in all the bio-flexyfilms.

***In-vitro* Drug Release:** The drug release study of formulated bio-flexy films is carried out by using the MS diffusion apparatus, which having two compartments (Upper compartment and lower compartment), the formulated bio-flexy films of 1 cm^2 from each formulation was attached on to the eggshell membrane which was bind to the donor compartment (upper compartment) at another end and this assembly was deep in a receptor compartment (lower compartment) having 10 ml of phosphate buffer solution (pH 6.5). Samples were withdrawn completely at fixed time intervals till 36 h and replaced by a fresh buffer. The samples were analyzed by UV Spectroscopy at λ_{max} of 216 nm, and percent cumulative drug release (% CDR) was calculated [25].

Stability Studies: The stability studies of the formulated bio-flexy films were determined for three months as per ICH guidelines at different temperatures and relative humidity. The formulated bio-flexy films were kept for stability studies in stability chamber at various conditions of temperatures and Relative Humidity (5 ºC ± 3 ºC /60% RH, at room temperature *i.e.,* 25 ºC ± 2 ºC /60% ±5% RH and at 40 ºC ± 2 ºC / 75% RH) for three months. The changes were observed in the characteristics of bio-flexyfilms, and the results were reported [26].

RESULTS AND DISCUSSION: *Phoenix dactylifera* biopolymer was observed as dark brown in color, which was reported to show the color-changing point at 214 ºC, and percentage yield was found to be 25%. The isolated biopolymer was found to be soluble in water, insoluble in alcohol, chloroform, and ether. The biopolymer showed a viscosity of 1.5cp with pH 7.2 and surface tension of 74.25 dyne/cm. *Phoenix dactylifera* biopolymer showed a positive reaction with Molisch's and Fehling reagent, hence proved the presence of carbohydrate in the polymer. The positive result in Ninhydrin, biuret, and iodine test indicates the presence of proteins and starch in the biopolymer.

Mucoadhesive Property of Isolated Polymer: The study for mucoadhesive of isolated biopolymer showed that there was no significant change in bond strength of 3% w/v HPMC and sodium CMC in comparison to 3% w/v isolated biopolymeric solution of *Phoenix dactylifera*. It was observed that an increase in the contact time showed improvement in the bioadhesive bond strength between biopolymeric solution and glass substrate; hence mucoadhesive of isolated biopolymer increased with time, as shown in **Fig. 2**.

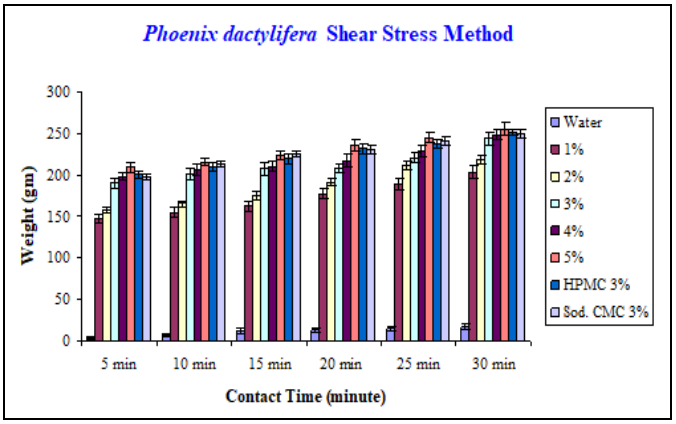

FIG. 2: SHEAR STRESS STUDY OF *PHOENIX DACTYLIFERA BIOPOLYMER*

Mucoretentive Property of Isolated Polymer: In MS Mucoretaintability method, *Phoenix dactylifera* biopolymer showed an appreciable dislodgement time of 197±1.00 min from labial mucosal substrate respectively and which was found to be more than the standard polymers of HPMC (190±1.00 min) and sodium CMC (165±2.00 minutes). Hence, the study revealed that *Phoenix dactylifera* biopolymer has better mucoadhesive property than HPMC and Sodium CMC with a good mucoretentive character.

Spectral Analysis of Isolated Biopolymer: The results of spectral analysis using IR spectrum for *Phoenix dactylifera* biopolymer reported peaks at 3389 cm^{-1} (OH stretching), 2931 cm^{-1} (C-H stretching alkane), 2362 cm^{-1} (C=C alkene), 1637 cm^{-1} amines (C=O stretching of carboxylic acid), 1247 cm^{-1}; 1070 cm^{-1} (C-N stretching) and 771cm^{-1} (CH bending aromatic ring) as given in **Fig. 3**.

The ^{1}H NMR spectrum of *Phoenix dactylifera* biopolymer showed chemical shift values at δ 1.58 ppm CH saturated proton), δ 3.1-3.7 ppm (-CH_3OR ether proton), δ 4.5 ppm (-C=CH vinylicproton) and δ5.1 ppm (ROH hydroxyl proton) as shown in **Fig. 4**.

The mass spectrum of *Phoenix dactylifera* biopolymer revealed parent peak at m/z value 219.1 as given in **Fig. 5**.

DSC thermogram of *Phoenix dactylifera* Phoenix showed glass transition temperature 135.31 ºC. Peak height was observed at 54.1757 mW, and the peak area was found to 7673.028 mJ. The value of delta was 767.3028 J/g as observed in **Fig. 6**.

The results of IR spectra of isolated biopolymer showed the presence of carboxylic, hydroxyl, and amino functional groups in the biopolymer. This clearly indicated that biopolymer possessed inbuilt mucoadhesive because mucoadhesive bonds are formed between these functional groups and mucin glycoproteins. ^{1}H NMR spectra of the isolated biopolymer revealed the presence of peaks with δ value 3-3.3 ppm, which indicates the presence of [$(OCH_2CH_2)_n$ O-CH_2-CH_2-CH_2- N $(CH_3)_2$-CH_2-$(CH_2)_{10}$-CH_3] group. The peaks at δ value 0.6-1.7 ppm showed the presence of [–CH_2-CH_2-] group. The peak at δ value 3.3-4.5 ppm revealed the presence of [$(OCH_2$-$CH_2)_n$-OCH_2-CH_2-OH] group. These groups indicated the polymeric nature of biopolymer.

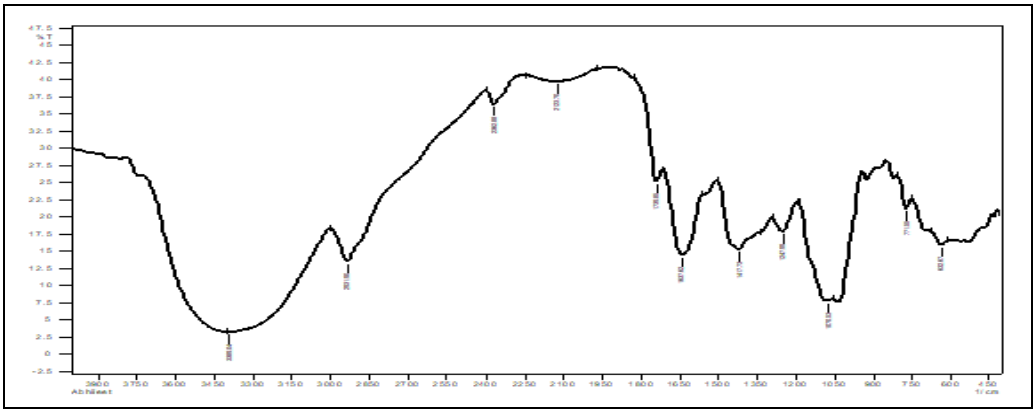

FIG. 3: IR SPECTRUM OF *PHOENIX DACTYLIFERA BIOPOLYMER*

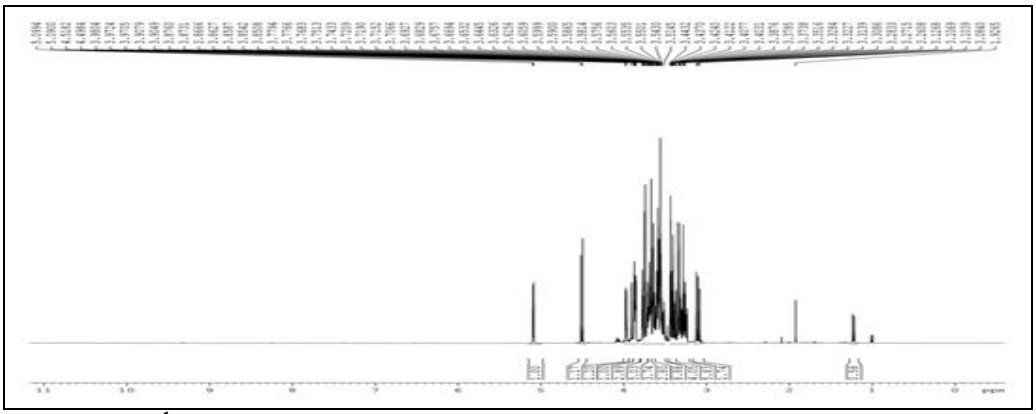

FIG. 4: ^{1}H NMR SPECTRUM OF *PHOENIX DACTYLIFERA BIOPOLYMER*

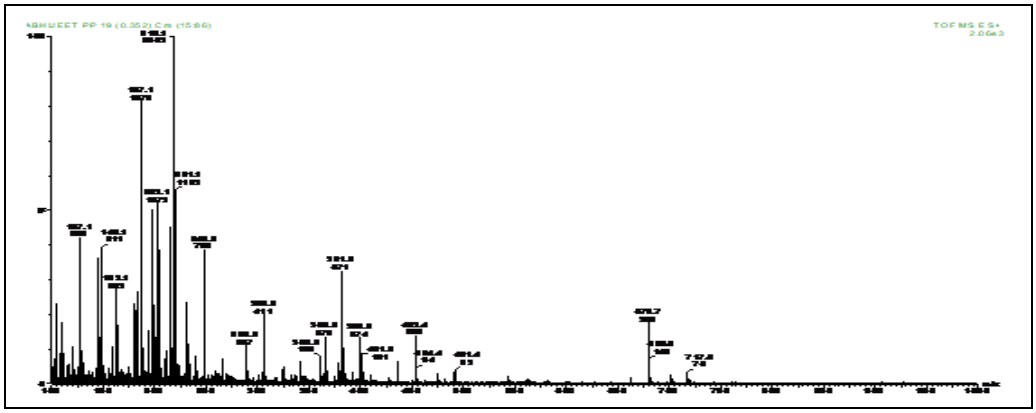

FIG. 5: MASS SPECTRUM OF *PHOENIX DACTYLIFERA BIOPOLYMER*

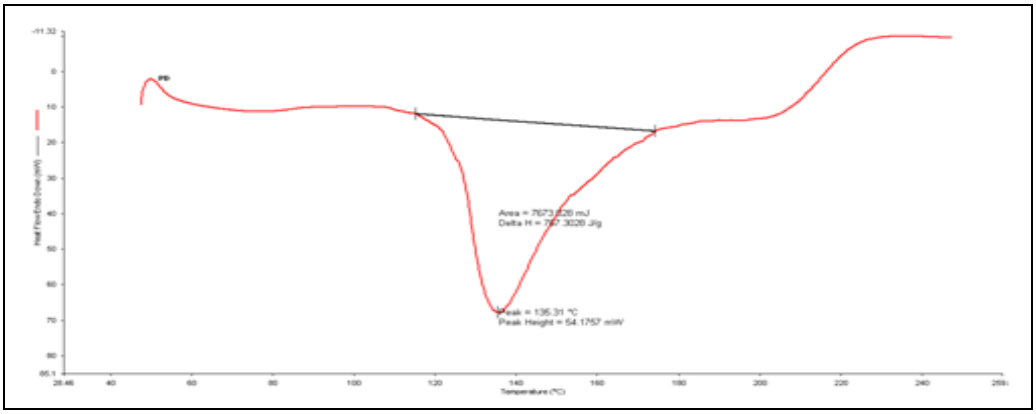

FIG. 6: DSC THERMOGRAM OF *PHOENIX DACTYLIFERA BIOPOLYMER*

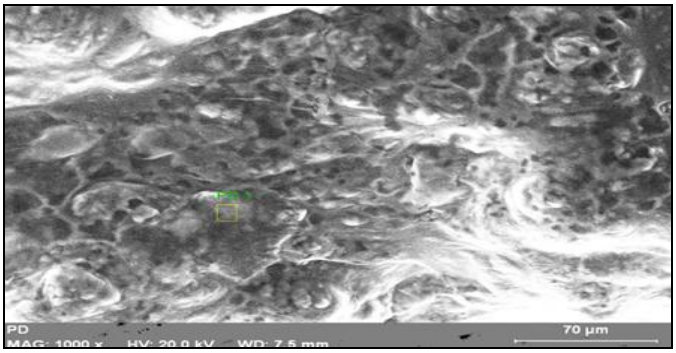

FIG. 7: SEM OF *PHOENIX DACTYLIFERA* BIOPOLYMER FOR SURFACE TOPOLOGY

SEM for Surface Topology of Isolated Biopolymer: The SEM image of the biopolymer revealed smooth and irregular topography as shown in **Fig. 7** and have amorphous nature, which provides a large surface area, thus giving enhanced solubility.

The elemental analysis showed that all the biopolymers had carbon and hydrogen as the major elements and were devoid of metal contamination of arsenic, lead, mercury etc., as given in **Fig. 8**. Thus, the study revealed that the isolated biopolymer had carbon and hydrogen as the major elements. The biopolymer was devoid of metal contamination like arsenic, lead, mercury, etc., as shown in **Table 2.**

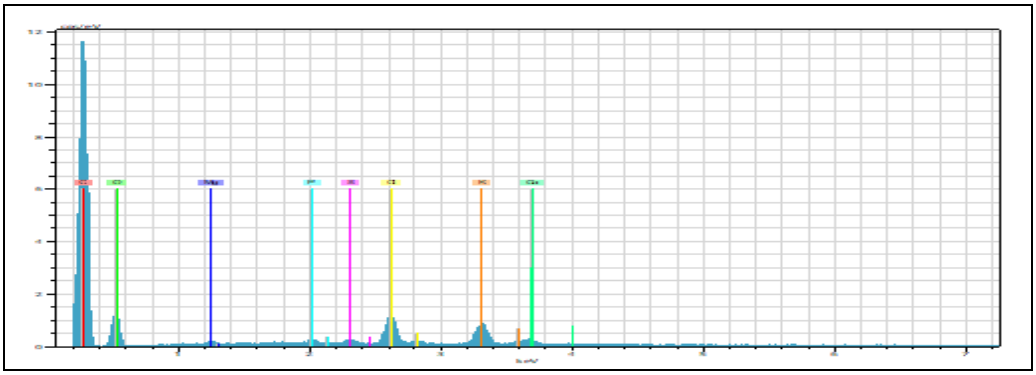

FIG. 8: ELEMENTAL ANALYSIS BY SEM FOR *PHOENIX DACTYLIFERA BIOPOLYMER*

TABLE 2: LIST OF ELEMENTS BY ELEMENTAL ANALYSIS FOR *PHOENIX DACTYLIFERA BIOPOLYMER*

Spectrum: PD						
Element	**Series**	**unn.C [wt.-%]**	**norm.C [wt.-%]**	**Atom.C [at.-%]**	**Oxide**	**Oxid. C [wt.-%]**
Carbon	K-series	0.00	0.00	0.00	CO2	0.00
Magnesium	K-series	0.10	0.10	0.07	MgO	2.84
Phosphorus	K-series	0.10	0.10	0.05	P2O5	3.88
Sulfur	K-series	0.14	0.14	0.07	SO3	6.03
Chlorine	K-series	2.06	2.06	0.95	Cl	34.27
Potassium	K-series	2.09	2.09	0.88	K2O	42.01
Calcium	K-series	0.47	0.47	0.19	CaO	10.98
Oxygen	K-series	95.03	95.03	97.77	O	1567.22

Acute Toxicity Studies: The acute toxicity studies performed for biopolymer of *phoenix dactylifera* showed results with no significant changes in bodyweight, weight, skin reaction, respiratory rate, salivation, corneal reflex, diarrhea, lethargic conditions, convulsion, and behavioral patterns. This showed that the prepared biopolymer was edible, biocompatible, and biodegradable and can be used as a carrier for delivery systems as transtibial route.

Standard Curve of Phenytoin: The standard curves of the drug prepared in labial pH (phosphate buffer pH 6.5), phosphate buffer pH 7.4, and methanol using UV-Visible Spectrophotometer (Shimadzu -1800) and showed the λ_{max} at 216 nm, 213 nm, and 218 nm respectively as given in **Fig. 9**. Thus, they are useful in performing the *in-vitro* release studies.

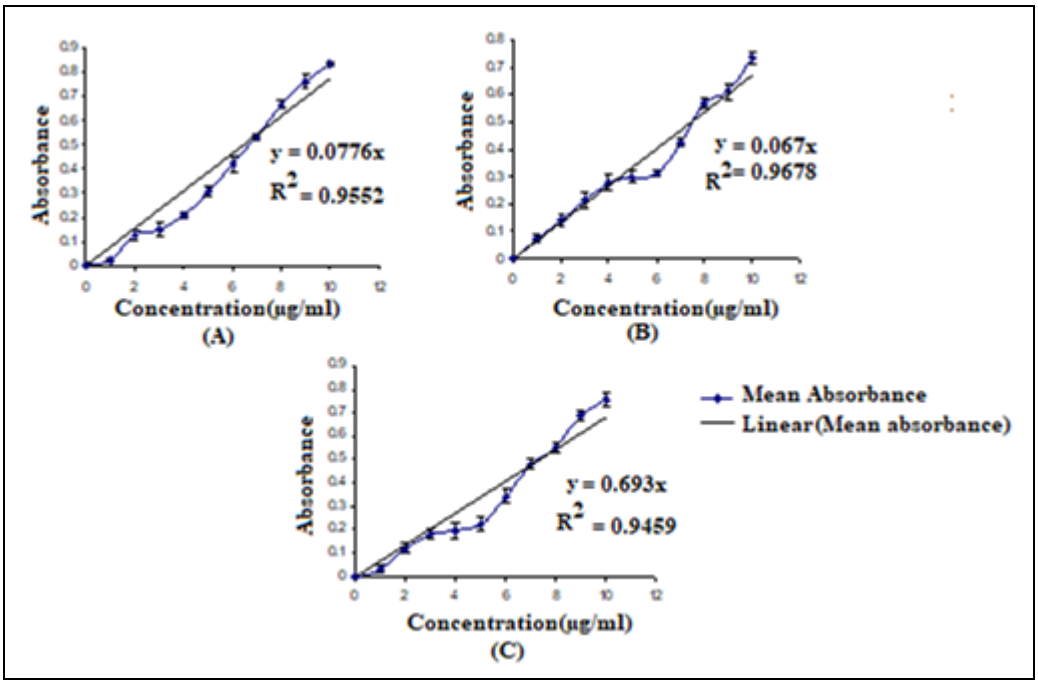

FIG. 9: CALIBRATION CURVE OF PHENYTOIN IN VARIOUS SOLVENTS; (A) pH 6.5 BUFFER, (B) pH 7.4 BUFFER, (C) METHANOL

Formulation and Evaluation of Phenytoin Loaded Bio-Flexy Films: The formulated bio-flexy films were smooth, translucent, and flexible without any sign of cracking. The weight of bio-flexy films ranged from 41.77 ± 0.61 mg to 82.45 ± 0.02 mg, and thickness ranged from 0.46±0.01 mm to 0.73±0.01 mm. The bio-flexy films showed folding endurance 132.00±1.73 to 183.00±1.00.

The swelling index of bio-flexy films ranged from 28.46±1.70 to 38.73±1.41. All bio-flexy films showed nearly neutral pH, as shown in **Table 3**.

The tensile strength of bio-flexy films from PD1 to PD6 was observed in the range of 91.32±0.99gto 142.44± 0.21g; percent elongation was in the range of 7.95±0.45 to 10.39±0.17%, percent moisture

uptake of bio-flexy films was found in the range of 6.26±0.06 to 11.25±0.26 % with percent moisture loss ranged from 6.85±0.11 to 11.27± 0.26 %. The vapor's transmission rate was in the range of 6.48±0.54 to 11.26±0.26 gm/cm^2/hr. The content uniformity for all bio-flexy films was determined, which varied from 90.63±0.52 to 97.28± 0.08% as given in **Table 4**.

TABLE 3: EVALUATION PARAMETERS OF PHENYTOIN LOADED BIO-FLEXY FILMS OF *PHOENIX DACTYLIFERA*

Formulation	Weight (mg)	Thickness (mm)	Folding endurance	Swelling index	Surface pH
PD1 (0.5%)	41.77±0.61	0.46±0.01	132.00±1.73	28.46±1.70	6.80±0.05
PD2 (1%)	46.10±0.59	0.46±0.01	142.33±2.51	29.10±1.26	6.30±0.15
PD3 (2%)	52.62±0.02	0.56±0.01	152.66±2.51	31.37±0.44	7.10±0.10
PD4 (3%)	57.33±0.03	0.59±0.01	160.66±0.57	32.97±0.21	6.96±0.11
PD5 (4%)	70.17±0.08	0.72±0.01	176.66±1.15	36.76±1.04	7.10±0.10
PD6 (5%)	82.45±0.02	0.73±0.01	183.00±1.00	38.73±1.41	7.10±0.10

TABLE 4: EVALUATION PARAMETERS OF PHENYTOIN LOADED BIO-FLEXY FILMS OF *PHOENIX DACTYLIFERA*

Formulation	Tensile strength (g)	Percent Elongation	Percent Moisture uptake	Percent Moisture loss	VTR (g/cm^2/h)	Percent drug content
PD1 (0.5%)	91.32±0.99	7.95±0.45	6.26±0.06	6.85±0.11	6.48±0.54	90.63±0.52
PD2 (1%)	106.88±0.57	8.38±0.14	9.23±0.11	9.26±0.35	7.23±0.07	91.17±1.04
PD3 (2%)	116.20±0.95	8.94±0.10	11.09±0.26	11.62±0.32	7.52±0.61	92.86±1.07
PD4 (3%)	124.07±0.75	9.29±0.24	10.42±0.13	11.85±0.71	8.64±0.25	93.64±0.71
PD5 (4%)	132.96±0.45	9.91±0.14	10.76±0.38	10.39±0.57	10.60±0.38	95.13±0.73
PD6 (5%)	142.44±0.21	10.39±0.17	11.25±0.26	11.27±0.23	11.26±0.26	97.28±0.08

***In-vitro* Drug Release:** The *in-vitro* release of bio-flexy films was determined in triplicate, and average of three readings was determined. The percentage release found in order of PD6 > PD5 > PD4 > PD3 > PD2 > PD1 as given in **Fig. 10**.

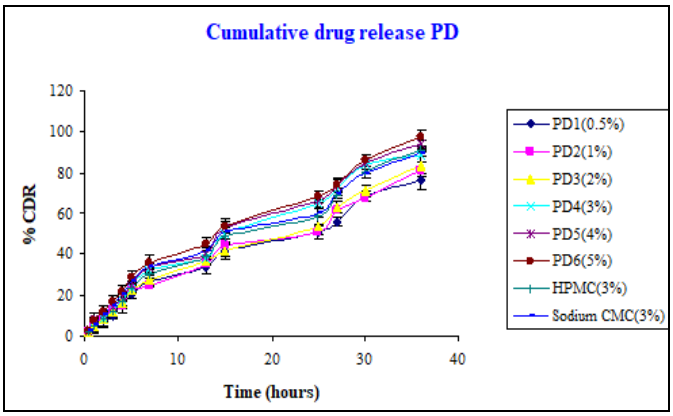

FIG. 10: *IN-VITRO* DRUG RELEASE OF PHENYTOIN LOADED BIOFILMS OF *PHOENIX DACTYLIFERA*

The percent release of PD6 bio-flexyfilm containing phenytoin and *Phoenix dactylifera* biopolymer was found to be showing the best drug release among all prepared bio-flexy films and was found to be 97.15±2.08%. The C_{max}, T_{max}, and AUC for PD6 bio-flexyfilm was found out to be 9.80 µg/ml, 8 h and 154.85µg h/ml, respectively. The reported values of phenytoin loaded in *Phoenix dactylifera* biopolymer were much better as compared to the phenytoin loaded in HPMC and sodium CMC (standard polymer).

The drug release kinetics of bio-flexy films was determined by "BIT-SOFT 1.12" software. The T_{50} value of phenytoin loaded bio-flexy films varied from 18.71 h to 29.90 h. The T_{80} value of phenytoin loaded bio-flexy films was in the range of 30.53 h to 43.03 h.

Stability Studies: The stability studies were performed according to ICH guidelines for the best formulation (PD6) showed no significant changes in the colour, odour or other properties of the bio-flexyfilms. On the basis of evaluation parameters for bio-flexy films and *in-vitro* drug release, R^2 value, $t_{50\%}$, $t_{80\%}$ for test and standard flexi film showed that PD6, was best among the prepared formulations. Hence it was concluded that bio-flexy films are stable at various conditions of temperature and humidity.

CONCLUSION: The work done for the formulation of phenytoin loaded in biopolymer (*Phoenix Dactylifera)* formulated into a bio-flexy films showed in-built film forming ability with appreciable mucoadhesivity. The work can be further extended in future for the treatment of chronic diseases. The future scope of labial delivery system is very a novel approach to develop various dosage forms as mucoadhesive tablet, mucoadhesive patches and mucoadhesive films, mucoadhesive *etc*.

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