IJPSR (2018), Volume 9, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 November, 2017; received in revised form, 25 January, 2018; accepted, 06 February, 2018; published 01 August, 2018

DESIGN AND *IN-VITRO* CHARACTERIZATION OF METADOXINE BUCCAL PATCHES USING *BORASSUS FLABELLIFER* FRUIT RESIN – A NOVEL MUCOADHESIVE POLYMER

V. Hariharshan * and M. Gopal Rao

Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore - 641044, Tamil Nadu, India.

Keywords:

Buccal patch, Palmyra palm fruit resin, *B. flabellifer*, Metadoxine

Correspondence to Author:
V. Hariharshan

Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore - 641044, Tamil Nadu, India.

E-mail: v.h_harshan92@yahoo.com

ABSTRACT: In this study, an attempt was made to introduce a new mucoadhesive polymer - *Borassus flabellifer* fruit resin (BFR), especially for buccal drug delivery. The novel polymer, in combination with two other natural polymers (Pectin and Sodium alginate) and one synthetic polymer (PVA) were used to formulate buccal patches containing Metadoxine. Compatibility studies carried out with the help of FT-IR spectrometer indicated that there are no chemical interactions between the drug and the polymers used. The calibration graph of Metadoxine was obtained by a validated UV spectrophotometric method at a λ_{max} of 324 nm. BFR was extracted from ripened palm fruit; stored and used for formulating 9 formulations in the ratios BFR : Pectin - 3:5, 4:4, 5:3 / BFR : SA - 4:2, 4:3, 4:4 and BFR : PVA - 3:5, 4:4, 5:3 respectively (the numbers in the ratios indicate the polymer concentration in percentage). Physicochemical properties such as thickness, weight variation, folding endurance, swelling index, surface pH, drug content and bioadhesion strength were evaluated appropriately and, the results were tabulated and compared. *In-vitro* diffusion study was also performed to examine the release pattern of the formulations, which was extended to determine the kinetics and mechanism of the release. Among the developed buccal patches, the formulation F7 with a polymer combination of 3% w/v BFR and 5% w/v PVA seems to be an optimized formulation, since it exhibits better folding endurance, uniformity of drug content, and comparatively better sustained-release of the drug.

INTRODUCTION: Tablets constitute around 70 - 80% of the total formulations available in the market. However, there are limitations which make tablets as a secondary option when formulating new drugs. This is attributed to the physicochemical properties as well as pharmacokinetic parameters of the drug intended for formulation such as aqueous solubility, bioavailability, absorption rate and half-life *etc*.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(8).3433-43

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(8).3433-43

Such limitations can be overcome by opting alternate routes of drug administration. Buccal drug delivery is one among them, which is studied extensively due to its ability to avoid the first-pass effect.

Buccal Drug Delivery: [1, 2] Buccal drug delivery is a newly adapted route of drug administration through the mucous membrane, lining the cheeks internally. Buccal drug delivery often involves a formulation which contains bio-adhesive or muco-adhesive material, which adheres to the buccal mucosa over a period of time and releases the drug. Both local and systemic drug action is possible by buccal route. There are two permeation pathways by which the drug gets transferred from the site of adhesion to systemic circulation.

They are paracellular (between the cells) and transcellular (across the cells) pathways. The permeating drug can adapt both the pathways simultaneously, but often through one pathway preferably than the other, depending on the physicochemical properties of the drug. The permeated drug gets absorbed into the reticulated vein which lies underneath the oral mucosa and gets transported through the facial veins, internal jugular vein, brachiocephalic vein and then drained into the systemic circulation.

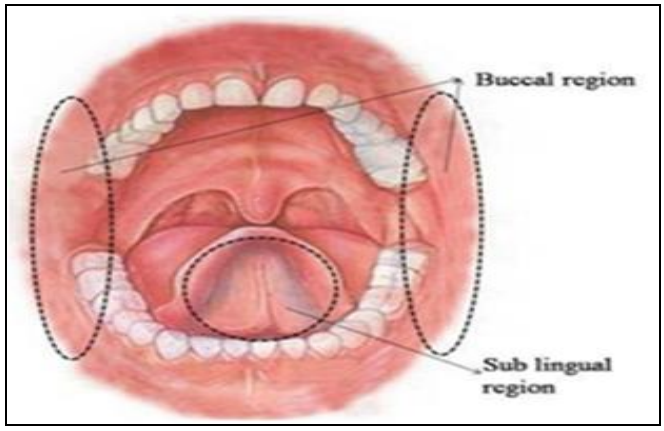


FIG. 1: ORAL CAVITY AND LOCATION OF BUCCAL MUCOSA

Palmyra Palm Fruit Resin - A Novel Mucoadhesive Polymer: Many natural and synthetic polymers such as HPMC, PVP, Carbopol, Eudragit, PVP, Pectin, Sodium alginate are employed so far to study their mucoadhesive and film-forming properties in a buccal drug delivery system. However, there is one underutilized polymer of natural origin, which is a resin obtained from ripe fruits of Palmyra palm, botanically named as *Borassus flabellifer* Linn.

Ravi Kumar *et al*., (2012), have isolated the mucilage obtained from unripe fruits (endosperms) of *B. flabellifer* and characterized it for its physical, thermal, sorption and functional properties [3]. In a different study, Ravi Kumar *et al*., (2012), have also studied the use of mucilage obtained from fruits of *B. flabellifer* as a natural gelling agent, using Diclofenac sodium as the model drug [4]. Vengaiah PC *et al*., (2015) [5], have studied B. flabellifer fruit pulp for its physicochemical properties. Saranya P and Poongodi Vijayakumar T, (2016) [6], have carried out a phytochemical screening of raw and thermally processed *B. flabellifer* fruit pulp.

Apart from the polymer, other ingredients of a buccal patch include, plasticizer, permeation enhancer, coloring agent, sweetening agent, flavoring agent and if required diluents [7]. The drug chosen for the study is Metadoxine, which is a hepatoprotective used in the treatment of acute and chronic alcoholism, and in the treatment of fatty liver- both alcoholic and non-alcoholic. It is also under study for the treatment of ADHD and Fragile X syndrome [8, 9]. Metadoxine is an ion pair of two compounds pyrrolidone carboxylic acid and pyridoxol, which efficiently eliminates alcohol and its byproducts from the body. Metadoxine is rapidly absorbed in the body exhibiting an absolute bioavailability of 60 - 80% and undergoes extensive tissue distribution. But the biological half-life of this drug is not more than 60 min [10]. Therefore, this work focuses on establishing the mucoadhesive property of *B. flabellifer* fruit resin and to increase the mean residence time of Metadoxine to prolong its activity, by incorporating it in a buccal drug delivery system, which is currently unavailable in the market.

MATERIALS AND METHODS:

Materials: Metadoxine was obtained from Apotex Research Pvt. Ltd., Bangalore, as a gift sample. Pectin, Sodium alginate and Polyvinyl alcohol (M.W: 160000)

Methods:

Pre-Formulation Studies:

Authentication of the Source of the Palm Fruit Resin: Various parts of the Palmyra palm such as fruits (unripe and ripen), leaf with stalk and flower were submitted for identification and authentication of the botanical source to the Botanical Survey of India, Southern Regional Centre, Coimbatore.

Preparation of *B. flabellifer* Fruit Resin (BFR): [6]

A ripened fruit of *B. flabellifer* was obtained from a local vendor. The black colored peel of the fruit was removed and the three seeds along with the fibrous pulp were partitioned. Each portion of the fruit was boiled in hot water at 40 °C. The sticky, yellow pulp was manually extracted from the fibers with the help of hot water. The process was continued till the fibers were free of yellow pulp and turn into pale color.

The seed and fibers were removed by means of filtration using a muslin cloth. The filtrate (fruit

pulp) was concentrated by evaporating the liquid (at not more than 45 °C), till the extract dried into a golden brown colored sticky resin. The process of drying must be done carefully, since the increase in temperature may char the product. The dried resin was stored in an air-tight container at room temperature.

Compatibility Studies using FT-IR: [11] Compatibility studies are essential to study the interaction of the excipients with the drug, because it is an important criterion for any excipient, not to exhibit any kind of interaction with the drug. A study was carried out using infrared spectrophotometer by KBr pellet press method to find out if there are any possible chemical interactions between drug and all the polymers used such as the new mucoadhesive polymer *B. flabellifer* fruit Resin (BFR), Pectin, Sodium alginate (SA) and PVA.

Preparation of Calibration Graph of Metadoxine using UV-visible spectrophotometry: [12] 10 mg of Metadoxine was dissolved in phosphate buffer solution (PBS) pH 6.8 and the volume was made up to 100 ml with the same, which gives a stock solution of 100 µg/ml. From this stock solution, aliquots of 0.4 - 4 ml were withdrawn using a pipette and transferred to a series of ten 10 ml standard flasks. The volumes were made up with PBS pH 6.8. Thus, the concentration range of 4 - 40 µg/ml was obtained.

The absorbance of the solutions were estimated at 324 nm using PBS pH 6.8 as reagent blank, with the help of UV-visible spectrophotometer. A triplicate of measurements was made to get mean absorbance values. A calibration graph of absorbance *vs.* concentration was plotted.

Formulation of Metadoxine Buccal Patches:

Optimization of Polymer Ratios: Almost 50 combinations of BFR with polymers such as Carbopol-940, HPMC. HEC, PVP, Gelatin, Pectin, Sodium alginate, PVA 6000, PVA 4000, PVA 125000, PVA 160000 were tried to formulate buccal patches of formidable physical properties, by adding varying volumes of plasticizer (PEG-400) and permeation enhancer (DMSO) [13]. Finally, 9 polymer ratios using Pectin, Sodium alginate and PVA-160000 were found to be suitable.

Dose Calculation: Usually, films or patches, either transdermal or buccal involves a dose calculation based on the surface area [14]. In this study, the 'thickness' factor is incorporated, enabling a more precise dose calculation, since the volume of the matrix is considered, *i.e.*, a patch is considered as a three-dimensional cylinder rather than a two-dimensional circle.

The average thickness of patches made up by 10 ml of formulation mixture without the drug, found out using a digital screw gauge, after a number of trials (during optimization of polymer ratios) is 0.07 cm. Therefore, the dose calculation proceeds as follows:

Volume of a parent patch made up by a particular volume of polymer mixture/matrix $= \pi R^2 h$

Volume of individual patch (final product) $= \pi r^2 h$

Where R = radius of parent patch; r = radius of individual patch

Volume of a parent patch made up by 10 ml of formulation mixture $= 3.1429 \times 4.4 \times 4.4 \times 0.07$
$= 4.2593\ cm^3$

Volume of a single patch of radius 1 cm
$= 3.1429 \times 1 \times 1 \times 0.07$
$= 0.22\ cm^3$

The number of possible patches (theoretically)
= (Volume of parent patch) / (Volume of individual patch) $= 4.2593/0.22$
$= 19.3605$

Thus, the quantity of drug to be added
= Number of theoretical patches × Dose of individual patch $= 19.3605 \times 250$ mg
$= 4.8401$ g

Formulation of Buccal Patches by Solvent Casting Method: [15] A weighed quantity of BFR was added to distilled water and dissolved using a magnetic stirrer set at 500 rpm to obtain a uniform solution. Nine formulations using Pectin (F1-F3), SA (F4-F6) and PVA (F7-F9) in varying proportions were added to each formulation. The rest of the ingredients such as sucrose (sweetening agent), Vanillin (flavoring agent), PEG-400 (plasticizer) and Dimethyl sulphoxide (permeation enhancer) were added in the order as given in the

Table 1. Finally, the required quantity of Metadoxine was added to the polymer matrices. The formulation mixtures were poured into Petri dishes of known diameter and allowed to air-dry at room temperature, by covering the dishes with a clean sieve or in a hot air oven at 30 ± 5 °C, till the patches form a smooth non-sticky surface.

TABLE 1: COMPOSITION OF METADOXINE BUCCAL PATCHES

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients					**(in mg)**				
Metadoxine	4840	4840	4840	4840	4840	4840	4840	4840	4840
BFR	300	400	500	400	400	400	300	400	500
Pectin	500	400	300	-	-	-	-	-	-
SA	-	-	-	200	300	400	-	-	-
PVA	-	-	-	-	-	-	500	400	300
Vanillin	60	60	60	60	60	60	60	60	60
Sucrose	300	300	300	300	300	300	300	300	300
					(in ml)				
Water	10	10	10	10	10	10	10	10	10
PEG	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
DMSO	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

The parent patches of each formulation were cut into uniform pieces of buccal patches of fixed diameter, using a fabricated stainless steel punch with sharp edges.

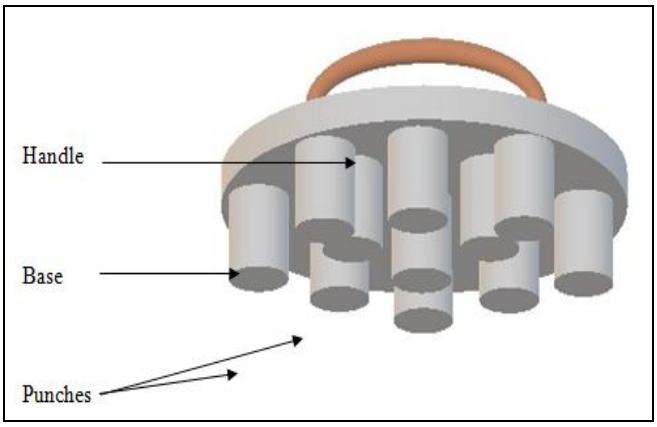


FIG. 2: FABRICATED PATCH CUTTER

Application of Backing Membrane: A suitable backing membrane prevents the buccal patch from releasing the drug through the non-adhering side. Hence, a backing membrane consisting of 4% PVA solution was sprayed over the dried patches only on one side [16].

Evaluation of the Metadoxine Buccal Patches:

Thickness: [17] The thickness must be measured before application of backing membrane. A sample patch from each formulation code was taken and measured for thickness at 5 different points using an electronic micrometer (digital screw gauge). Mean thickness and standard deviation values were calculated from the observed readings.

Weight Variation Test: [18] The same condition as above, measurement before application of backing membrane is followed. A random sample of 5 patches was taken from each formulation code and their individual weights were recorded. Mean weight and standard deviation values for each formulation were calculated.

Folding Endurance: [19] Folding endurance was determined by repeatedly folding a patch at the same point till the patch breaks into halves completely. The number of times the patch was folded till the point of break is considered as a patch's folding endurance.

Swelling Index: [20] Swelling index is directly related to the bioadhesive strength of a patch. One patch from each formulation code was taken in a pre-weighed basket made up of stainless steel mesh. The weights of each basket with patches were recorded. The baskets were placed in beakers; marked F1-F9; containing 4ml of PBS pH 6.8 each.

After 10 min, the baskets were removed from the beakers, the residual buffer solution was thoroughly strained and the weights were again noted.

Swelling index for each formulation was calculated by the following equation.

Swelling index = (Weight after swelling -Initial weight) / (Initial weight)

Surface pH: [21, 22, 23] A patch from each formulation code was placed in Petri dishes, and they were wetted with 1 ml of demineralized water and allowed to equilibrate for 30 min. The surface pH of each patch was measured by placing the tip of the pH meter electrode on the surface of the patch and holding for at least 10 min, till the pH value attains equilibrium. The procedure was repeated twice more to obtain average surface pH and standard deviation values.

Drug Content Assay: [24] Drug content assay was carried out by dissolving the patch completely in 50 ml of PBS pH 6.8, with the help of sonicator. Then, the volumes were made up to 100 ml with PBS pH 6.8. The solution is filtered. 1 ml of this filtrate was further diluted to 100 ml with PBS pH 6.8 and the absorbance was measured at λ_{max} of 324 nm. The concentration of the solution was determined from the calibration graph, by interpolation. The drug content is determined by the following steps:

Amount of drug present in a single patch (in mg) = (Concentration from the graph × Dilution factor) / 1000

Assay / Percentage purity = (Amount of drug present) / (Labelled claim) × 100

Where the dilution factor = 10000
Labelled claim = 250 mg

***In-vitro* Bioadhesion Study:** [25]

Fabrication of the Test Assembly: The working double beam balance formed the basis of the fabricated bioadhesion test apparatus. The left side pan was removed and replaced with a stainless steel wire (A) of gauge 1.2 mm, hung with a Teflon coated glass tube (B) of diameter 1cm, loaded with weights to equate the right side pan. The height of the total setup was adjusted to accommodate a Teflon block (E), of height 1.5 cm and diameter 3.8 cm with an upward protrusion of 1 cm height 1.5 cm diameter on one of its face, leaving a headspace of 0.5 cm. The two sides were balanced so that the right side was 5 g heavier than the left.

Measurement of Adhesion Force: The pig's buccal mucosa (D) was excised, washed and was tightly tied over the protrusion of the Teflon block, with the mucosal side facing upwards. The setup was placed in a glass beaker (F) with sufficient quantity of PBS pH 6.8, such that the buffer reaches the surface of the mucosal membrane and keeps it moist. This beaker was placed on the left side of the balance. A patch (C) was stuck onto the Teflon coated tube (B) with a drop of water and the beam is raised by removing the 5 g weight from the right side pan.

This lowered the Teflon coated tube (B) along with the patch over the mucosa, with a weight of 5 g. The balance was kept in this position for 3 min and then weights were added gradually on the right pan till the patch gets separated from the mucosal surface completely. The excess weights of the pan *i.e.*, the total weight subtracted by 5, gives the measure of the force of detachment of the patch in grams.

The force required to detach the patch from the animal's tissue is directly proportional to the bioadhesion strength of the patches. Thus, the bioadhesion strength in Newton (N) can be calculated by

Force of adhesion (N) = {Force of detachment (g)} / 1000 × 9.81

FIG. 3: FABRICATED BIOADHESION TEST ASSEMBLY

A: Stainless steel wire
B: Teflon coated glass tube with weights
C: Metadoxine buccal patch
D: Pig buccal mucosa tissue
E: Teflon block
F: Glass beaker

The procedure was repeated for one patch from each formulation code. A fresh portion of tissue was used for each measurement.

***In-vitro* Diffusion / Permeation Study:** [18, 25, 26] *In-vitro* drug diffusion studies were performed by using Franz diffusion cell. It consists of a donor

compartment and a receptor compartment. The receptor compartment is filled with 16 ml of PBS pH 6.8 as the diffusion medium along with a magnetic bead. Over the filled receptor compartment, cellulose nitrate membrane of pore size 0.2 µm was placed and allowed to moisten for 1 min, to mimic buccal mucosa environment. Then a patch under study was placed over the membrane and closed tightly with the donor compartment. The whole assembly is fixed over a hot plate magnetic stirrer and the medium in the receptor compartment was subjected to stirring at 100 rpm and the temperature of the diffusion cell is supplied constantly with flowing hot water at 37 ° ± 1 °C to simulate the fluid and thermodynamics of the buccal environment.

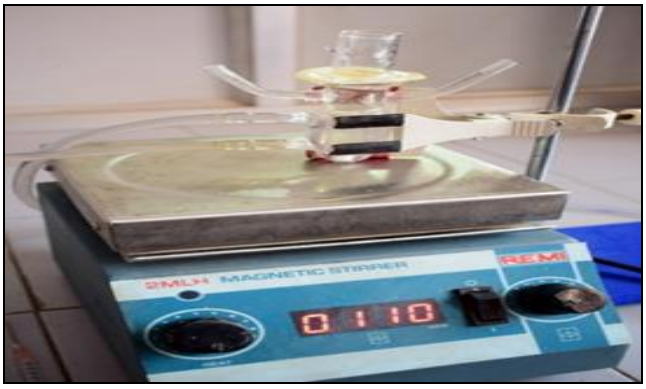


FIG. 4: FRANZ DIFFUSION CELL

One ml samples were withdrawn from the sample port at predetermined time intervals with the help of a 1ml disposable syringe and the same volume was replaced with PBS pH 6.8. The samples were suitably diluted with the same medium and are analyzed for drug content at 324 nm, using PBS pH 6.8 as the reagent blank. The unknown concentrations of the samples were obtained from the calibration graph of Metadoxine. The procedure is repeated for a sample patch from all formulations. The cumulative percentage release values for the respective time are tabulated **Table 6** and cumulative percentage release (%) *vs* time plots are drawn **Fig. 8**.

***In-vitro* Drug Release Kinetics:** [27] The order and mechanism of drug release kinetics of Metadoxine buccal patches were analyzed using the *in-vitro* diffusion study data, by plotting different kinetic models such as zero order, first order and Higuchi equations. The release pattern was determined using Korsmeyer - Peppas equations.

The exponent 'n' in Korsmeyer - Peppas equation can be calculated from the slope of the linear graph of log cumulative percentage of drug released (log Q) *vs*. log time (log t). The 'n' value is used to characterize the diffusion mechanism based on the data in **Table 2.**

TABLE 2: DIFFUSION EXPONENT AND DIFFUSION MECHANISM

Diffusion exponent	Overall diffusion mechanism
0.5	Quasi Fickian diffusion
0.5	Fickian diffusion (Higuchi Matrix)
0.5 < n < 1.0	Non-Fickian diffusion
1.0	Case 2 transport
>1.0	Super case 2 transport

Software such as DD Solver and Kinet DS are specifically programmed for calculating kinetic models. In this study, DD Solver was used to propagate respective graphs of each model, using cumulative percentage release per time data.

RESULTS:

Preformulation:

Authentication of Source of the Palmyra Palm Fruit Resin: The source of the Palmyra palm resin was authenticated as the fruit pulp of *Borassus flabellifer* L. belonging to family Arecaceae [28].

Preparation of the *Borassus flabellifer* Fruit Resin:

FIG. 5: *B. FLABELLIFER* FRUIT RESIN

Compatibility Studies using FT-IR [29]: The physical mixtures of Metadoxine and polymers were subjected to FT-IR analysis to identify any interaction between them. Wave numbers for individual compounds and physical mixtures were compared in **Table 3**.

Preparation of Calibration Graph of Metadoxine using UV-visible Spectrophotometry: The mean absorbance values for the standard concentrations of Metadoxine are given in the **Table 4**. It was found that the concentration of Metadoxine in the range 4 - 40µg/ml obeyed Beer-Lambert's law. The correlation coefficient was found to be 0.997862.

TABLE 3: INTERPRETATION OF IR SPECTRA OF DRUG, POLYMERS AND PHYSICAL MIXTURES

Functional group assignment	Standard wave number (cm^{-1})	Test wave number of Metadoxine (cm^{-1})	Test wave number of polymers (cm^{-1})				Test wave number of mixtures (cm^{-1})			
			BFR	Pectin	Sodium alginate	PVA	BFR + Drug	Pectin + Drug	Sodium alginate + Drug	PVA + Drug
O-H stretching	3200-3550	3462.56	3470.28	3531.99	3468.35	3467.38	3468.35	3463.53	3467.38	3468.35
N-H stretching (aliphatic)	3310-3350	3327.57	-	-	-	-	3330.46	3328.53	3327.57	3335.28
C=O stretching	2500-3300	2870.52	2924.52	2912.95	2927.41	2869.56	2871.49	2881.13	2866.67	2867.63
C-H bending	1650-2000	1900.5	1900.5	1900.5	1899.54	1902.43	1901.47	1898.58	1900.5	1901.47
C=O stretching	1705-1725	1667.16	1675.84	1658.48	1656.55	1658.48	1671.02	1661.37	1697.05	1673.91
N-H stretching (aromatic)	1266-1342	1281.47	-	-	-	-	1278.57	1280.5	1285.32	1279.54

There was no appearance or disappearance of any characteristic peak of the drug in any IR spectra obtained, which confirms the absence of chemical interaction between drug and the polymers.

TABLE 4: CALIBRATION GRAPH OF METADOXINE

S. no.	Concentration (µg/ml)	Absorbance
1	4	0.1587
2	8	0.1954
3	12	0.3350
4	16	0.4220
5	20	0.5418
6	24	0.6303
7	28	0.7253
8	32	0.8514
9	36	0.9826
10	40	1.0630

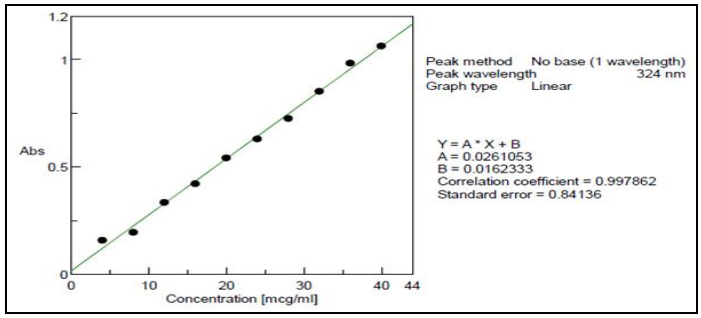
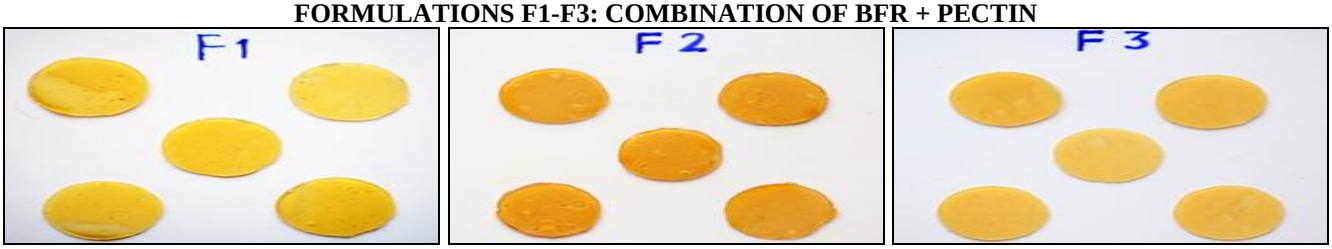


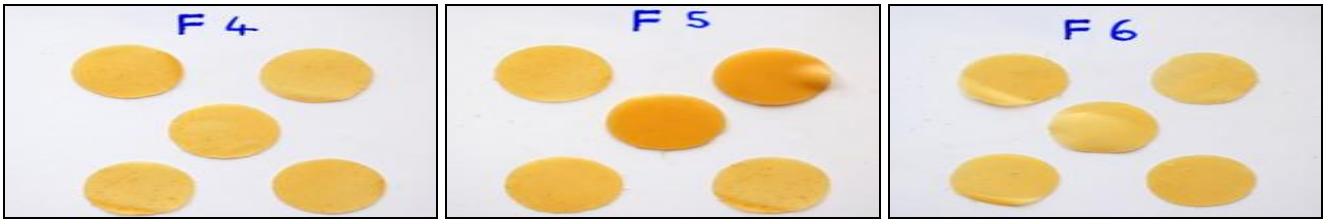
FIG. 6: CALIBRATION GRAPH OF METADOXINE

Formulation of Metadoxine Buccal Patches:

FORMULATIONS F1-F3: COMBINATION OF BFR + PECTIN



FORMULATIONS F4, F5 & F6: COMBINATION OF BFR + SODIUM ALGINATE



FORMULATIONS F7, F8 & F9: COMBINATION OF BFR + PVA

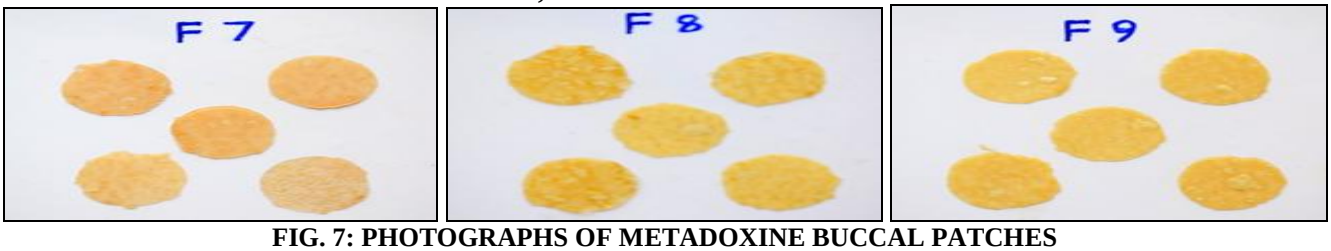


FIG. 7: PHOTOGRAPHS OF METADOXINE BUCCAL PATCHES

Evaluation of Metadoxine Buccal Patches:

Evaluation of Physicochemical Properties: The results of physicochemical evaluation tests such as thickness, weight variation, folding endurance swelling index, surface pH, drug content assay, bioadhesion strength and in-vitro drug release are given as follows:

TABLE 5: PHYSICOCHEMICAL EVALUATION TEST RESULTS OF METADOXINE BUCCAL PATCHES F1-F9

Formulation code	Thickness (mm)	Weight variation (mg)	Folding endurance	Swelling Index	Surface pH	Bioadhesion strength (N)	Drug content assay (%)
F1	0.7318 ± 0.02	425.8 ± 3.77	61	3.8125	6.83 ± 0.1	0.0183	97.6
F2	0.7294 ± 0.03	383.6 ± 4.39	16	0.6279	6.56 ± 0.08	0.0086	94
F3	0.6882 ± 0.02	399.6 ± 3.84	53	0.5152	6.51 ± 0.34	0.0398	90
F4	0.6978 ± 0.01	343.4 ± 4.21	56	4.0909	7.34 ± 0.09	0.0256	95.2
F5	0.7536 ± 0.01	350.2 ± 4.32	81	2.5857	6.84 ± 0.06	0.0360	96.8
F6	0.7190 ± 0.09	361.2 ± 3.11	152	4.0667	5.99 ± 0.11	0.0392	85.6
F7	0.7658 ± 0.02	399.8 ± 3.11	256	1.5455	7.17 ± 0.13	0.0187	99.6
F8	0.7152 ± 0.06	390.6 ± 3.28	230	0.6154	7.06 ± 0.09	0.0144	100.8
F9	0.6912 ± 0.03	386.8 ± 4.43	178	0.3571	6.89 ± 0.04	0.0271	96

TABLE 6: *IN-VITRO* PERMEATION DATA OF FORMULATIONS F1- F9

S. no	Time (h)	Cumulative percentage release (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	0.5	1.64	3.49	3.57	1.56	2.12	2.73	1.72	4.15	6.86
3	1.0	6.56	13.98	5.65	4.24	5.57	3.07	3.26	6.23	9.18
4	1.5	12.96	15.63	7.143	15.93	18.39	4.76	10.32	11.59	11.52
5	2.0	18.71	17.84	16.58	28.75	26.98	5.24	10.81	23.56	15.08
6	2.5	19.69	37.84	31.43	37.98	42.61	9.98	12.17	39.58	31.83
7	3.0	20.35	42.16	50.71	51.69	54.00	12.4	14.04	40.21	36.19
8	3.5	38.73	47.78	58.73	65.54	63.21	24.77	33.14	47.65	40.86
9	4.0	46.54	55.09	63.21	74.65	70.02	38.68	36.61	59.10	47.98
10	4.5	59.58	69.32	70.22	83.62	81.09	52.32	40.29	76.09	58.65
11	5.0	73.9	79.36	75.68	88.82	85.64	72.26	55.09	88.64	64.72
12	5.5	80.6	87.23	86.98	-	90.08	85.41	63.74	95.12	73.69
13	6.0	92.6	96.84	91.23	-	93.21	-	72.35	-	88.51

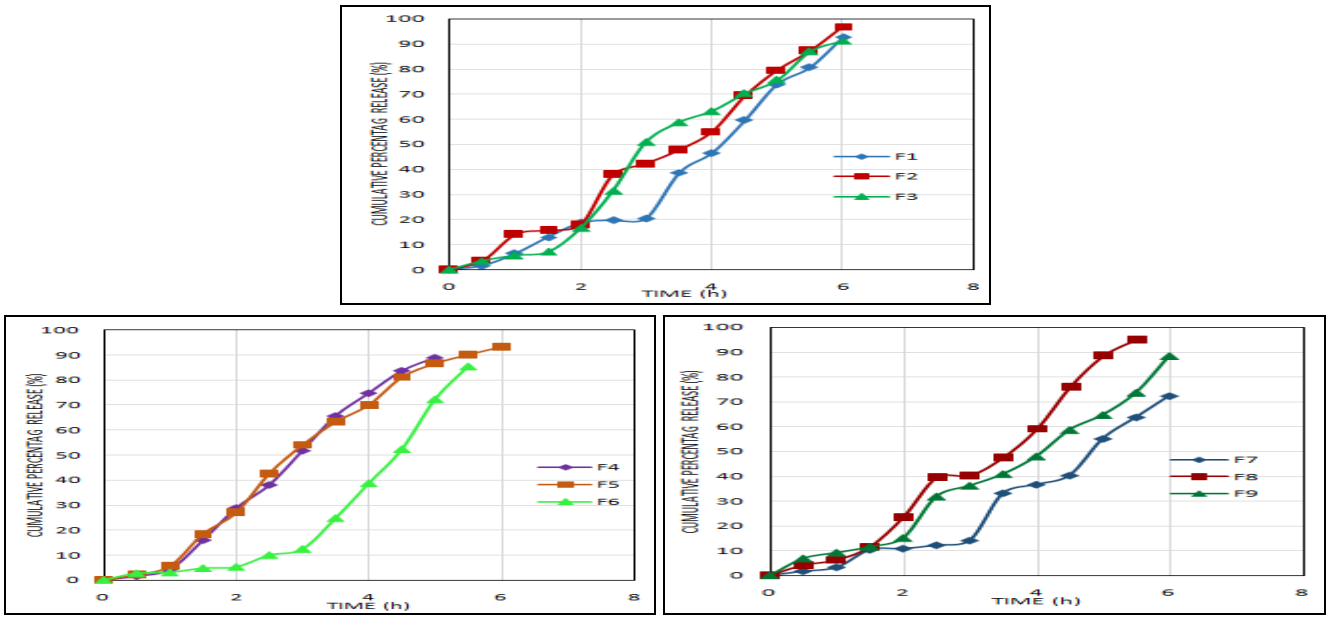
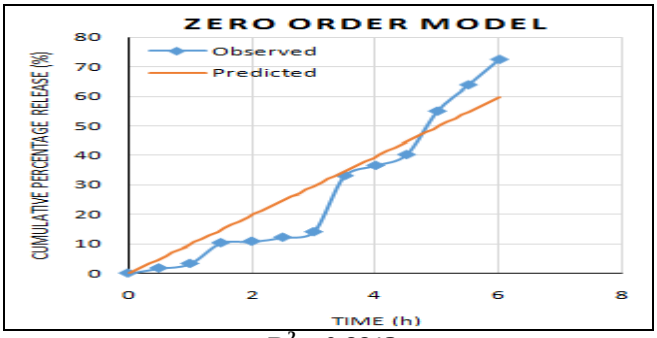


FIG. 8: *IN-VITRO* DIFFUSION PROFILE OF FORMULATIONS F1-F9

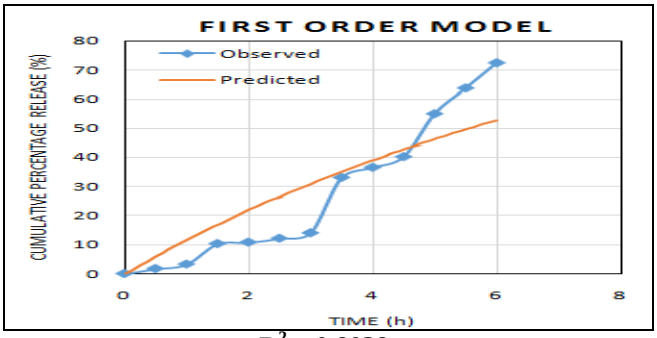
***In-vitro* Release Kinetics Study:** Correlation coefficient values of various kinetic models with respect to the *in-vitro* diffusion study were tabulated **Table 7** to determine the best-fit model and the mechanism of diffusion. The plots representing the models of optimized formulation F7 are depicted in **Fig. 9**.

TABLE 7: CORRELATION OF COEFFICIENT VALUES VARIOUS KINETIC MODELS

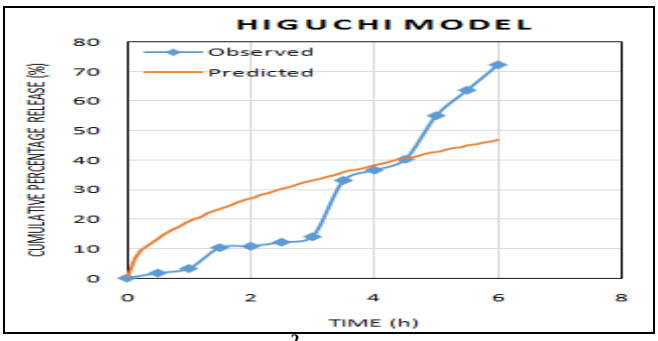
Formulation Code	Correlation coefficient value (R^2)			'n' values
	Zero order kinetic Model	First order kinetic Model	Higuchi's Model	Korsmeyer - Peppas Model
F1	0.9064	0.7947	0.6654	1.359
F2	0.9718	0.8670	0.7704	1.1171
F3	0. 9516	0.8590	0.7497	2.0805
F4	0.9583	0.8608	0.7456	2.2339
F5	0. 9732	0.8952	0.8099	2.0333
F6	0. 7536	0.6599	0.4996	1.9182
F7	0.8813	0.8028	0.6351	1.6159
F8	0.9485	0.8365	0.7262	1.6548
F9	0.9625	0.8760	0.7533	1.3261
Average	0.9381	0.8279	0.7061	1.7043
Standard deviation	± 0.04	± 0.07	± 0.09	± 0.38



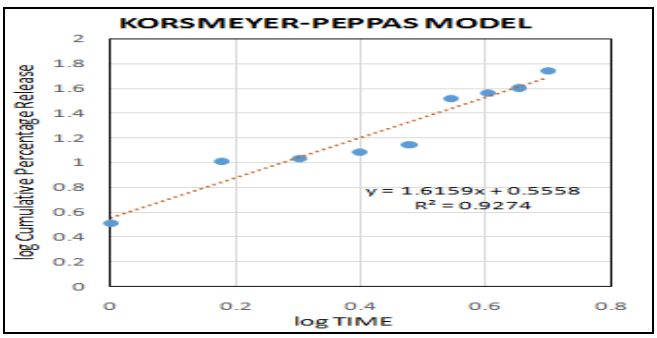
R^2 = 0.8813



R^2 = 0.8028



R^2 = 0.6351



n = 1.6159

FIG. 9: KINETIC MODELS OF DRUG RELEASE FROM F7

DISCUSSION:

- The thickness of the patches ranges from 0.6882 ± 0.02 mm to 0.7658 ± 0.02 mm, which ascertains that the average thickness assumed (0.7mm) for dose calculation is valid.
- The weights of the patches were in the range of 343.4 ± 4.21 mg to 425.8 ± 3.77 mg, whereas the intra-batch variation is relatively smaller with a maximum standard deviation of 4.43 mg (F9).
- The patches F7-F9 exhibited remarkable folding endurance with values as high as 256. Increase in the additional polymer (Pectin / SA/PVA) increases the folding endurance.
- Swelling index of all the formulations was relatively good, with highest swelling property exhibited by F4 (BFR: SA - 4:2) at 4.099.
- The surface pH values of the formulations were in the range 5.99 ± 0.11 to 7.34 ± 0.09, which indicates the patches have a similar pH to that of saliva (pH 6.8) and thus they will not irritate the buccal mucosa.
- The patch with highest bioadhesion strength (0.0398 N) was exhibited by F3 (BFR: Pectin – 5:3). This indicates that high concentration of BFR can help to retain the patch over the mucosa for a longer period, in spite of the mechanics of the facial tissues.

- The test for drug content resulted in assay values as high as 100.8% w/w and not less than 85.6% w/w, which proves that the method employed for formulation and dose calculation was appropriate and has good reproducibility.

- *In-vitro* permeation studies revealed that the formulation F7 (BFR: PVA- 3:5) exhibits a reasonable sustained release of more than 6 hrs and hence PVA is a suitable combination for BFR in developing a sustained release drug delivery system.

- The release kinetic modeling shows that the formulated Metadoxine buccal patches undergo zero order kinetic release since the correlation coefficient values corresponding to zero order model of all the formulations are comparatively higher and closer to 1.0 (averaging at 0.9381±0.04) than First order and Higuchi models.

- The Korsmeyer-Peppas modeling helped to determine the release mechanism of the buccal patch formulations as 'super case-2 transport' (according to **Table 2** and **7**) since the average 'n' exponent value is 1.7043 ± 0.38.

CONCLUSION: Metadoxine buccal patches were formulated and evaluated successfully by solvent casting method; following standard operating procedures. The evaluation tests revealed that *B. flabellifer* fruit resin is a suitable polymer for developing a buccal drug delivery system with reasonably extended release of the drug. Among the developed buccal patches, the formulation F7 with a polymer combination of 3% w/v BFR and 5% w/v PVA seems to be an optimized formulation, since it exhibits better folding endurance, uniformity of drug content, and moderate sustained release of the drug. Therefore, Metadoxine which exhibits lower elimination half-life can be incorporated in buccal drug delivery systems, in order decrease the dose frequency and thereby decreasing the possibility of dose dumping. It also should be noted that concentration of BFR is directly proportional to the bioadhesion strength and hence BFR justifies its selection as a novel mucoadhesive polymer of natural origin.

ACKNOWLEDGEMENT: We would like to thank Mr. Suhas and Mr. Rajesha. B.C, Apotex Research Pvt. Ltd., Bangalore for being generous enough to provide us with the gift sample of Metadoxine and Mr. M. Vaithilingam for being instrumental in suggesting the use of this plant source, to be developed into a research work.

CONFLICT OF INTEREST: The authors have no conflicts of interest with regard to the content this research article.

REFERENCES:

1. Namita S and Garg MM: Current status of Buccal Drug Delivery System: A review. Journal of Drug Delivery and Therapeutics 2015; 5(1): 34-40.
2. Nicolini MM and Morales JO: Overview and Future Potential of Buccal Mucoadhesive Films as Drug Delivery Systems for Biologics. AAPS Pharm Sci Tech, 2017; 18(1): 3-14.
3. Ravi Kumar, Rajarajeshwari N and Swamy NVB: Isolation and Characterization of Borassus flabellifer Mucilage. Research Journal of Pharmacy and Technology, 2012; 5(8): 1093-1101.
4. Ravi Kumar *et al*.: Exploitation of Borassus flabellifer fruit mucilage as a novel natural gelling agent. Der Pharmacia Lettre, 2012; 4(4): 1202-1213.
5. Vengaiah. PC *et al*.: Physico-chemical Properties of Palmyrah fruit pulp (*Borassus flabellifer* L). Journal of Nutrition & Food Science 2015; 5: 391.
6. Saranya P and Poongodi VT: Preliminary phytochemical screening of raw and thermally processed Palmyra palm (*Borassus flabellifer* Linn.) fruit pulp. Journal of Innovations in Pharmaceuticals and Biological Sciences 2016; 3(1): 186-193.
7. Kakar S, Prasad N and Singh R: A Review on Buccal Patches. In noriginal International Journal of Sciences, 2016; 3(5): 4-8.
8. De la Tijera FH *et al*.: Metadoxine improves the three and six-month survival rate in patients with Chronic alcoholic hepatitis. World Journal of Gastroenterology 2015; 21(15): 4975-4985.
9. Addolorato G *et al*.: Metadoxine in the treatment of acute and chronic alcoholism: a review. International Journal of Immunopathology and Pharmacology 2003; 16(3): 207-214.
10. Kaizer M *et al*.: Review of Salient Investigational Drugs for the Treatment of Fragile X Syndrome. Journal Child and Adolescent Psychopharmacology 2017; 27(10): 850-863.
11. Skoog DA, Holler FJ and Crouch SR: Application of Infrared Spectrometry, Principles of Instrumental Analysis. 2007; 6: 455-477.
12. Pradeep Kumar *et al*.: Derivative spectroscopy: Development and validation of new spectroscopic method for the estimation of Metadoxine in bulk and solid dosage form. Oriental Journal of Chemistry, 2008; 24(1): 313-317.
13. Ogaji IJ, Nep EI and Audu-Peter JD: Advances in natural polymers as Pharmaceutical Excipients, Phamaceutica Analytica Acta 2011; 3(1): 1-16.
14. Saraswathi B, Anna B and Umashankar MS: Polymers in Mucoadhesive Drug Delivery System-Latest Updates. International Journal of Pharmacy and Pharmaceutical Sciences 2013; 5(3): 423-430.

15. Shivhare UD, Suruse PB and Varvandkar SS: Formulation and Evaluation of Buccal Patch containing Aceclofenac. Journal of Applied Pharmacy 2014; 6(1): 65-76.
16. Swathi G *et al*.: Salbutamol Buccal Patches to treat blood pressure. International Journal of Biopharma Research 2013; 2(3): 99-103.
17. Singh R, Sharma D and Garg R: Review on Mucoadhesive Drug Delivery System with Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery System for the Effective Delivery of Pharmaceuticals. Journal of Developing Drugs 2017; 6(1): 1-12.
18. Augusthy AR *et al.:* Formulation and Evaluation of Rabeprazole Buccal Patches. Journal of Pharmaceutics and Nanotechnology 2014; 3(1): 125-136.
19. ÖzyazıcıM *et al*.: Bioadhesive gel and Hydrogel systems for Buccal delivery of Ketoprofen: Preparation and *in vitro* Evaluation Studies. American Journal of Drug delivery and Therapeutics 2015; 2(3): 78-91.
20. Koyi PK and Khan AB: Buccal Patches: A Review. International Journal of Pharmaceutical Sciences and Research 2013; 4(1): 83-89.
21. Bhattacharjee S, Nagalakshmi S and Shanmuganathan S: Design, Development and Evaluation of Mucoadhesive film for water-insoluble drug using different plasticizers. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(3): 107-110.
22. Rao NGR, Shravani B and Reddy MS: Overview on Buccal Drug Delivery Systems. Journal of Pharmaceutical Sciences and Research 2013; 5(4): 80-88.
23. Mujoriya R *et al*.: A Review on study of Buccal Drug Delivery System. Innovative Systems Design and Engineering, 2014; 2(3): 18-31.
24. Reddy PC *et al*.: Development, optimization and *in vivo* characterization of domperidone-controlled release hot-melt-extruded films for buccal delivery. Drug Development and Industrial Pharmacy 2016; 42(3): 473-484.
25. Ayachat AM, Gujar KN and Wagh KV: Development and evaluation of Tamarind seed Xyloglucan-based mucoadhesive buccal films of Rizatriptan benzoate. Carbohydrate Polymers 2013; 91(2): 537-542.
26. Khdair A *et al*.: *In-vitro* artificial membrane-natural mucosa correlation of Carvedilol buccal delivery. Journal of Drug Delivery Science & technology 2013; 23(6): 603-609.
27. Shaikh HK, Kshirsagar RV and Patil SG: Mathematical Models for Drug Release Characterization: A Review. World Journal of Pharmacy and Pharmaceutical Sciences 2015; 4(4): 324-338.
28. Hooker JD: Flora of British India 6: 482.
29. Silverstein RM: Spectrometric identification of Organic compounds 6: 79-99.

How to cite this article:
Hariharshan V and Rao MG: Design and *in-vitro* characterization of metadoxine buccal patches using borassus flabellifer fruit resin – a novel mucoadhesive polymer. Int J Pharm Sci & Res 2018; 9(8): 3433-43. doi: 10.13040/IJPSR.0975-8232.9(8).3433-43.