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Preparation and Characterization of Metadoxine Buccal Patches

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Abstract

Natural polymers are trending as a reliable alternative for synthetic and semi synthetic polymers, in the development of a large number of novel drug delivery systems. One such new alternative to be used as a mucoadhesive polymer- B. flabellifer Fruit resin, especially for buccal drug delivery was introduced. The novel polymer, in combination with two other natural polymers (Pectin & Sodium alginate) and one synthetic polymer (PVA), was used to formulate a buccal drug delivery system containing Metadoxine. This drug was chosen due to its low half-life (maximum of 60 min) and attempt was made to reduce its dose by sustaining its release. Also alcoholism is a serious social and health issue affecting a significant amount of world population and hence a therapeutic alternative to cure alcoholism is a need of the hour. 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, including BFR. The calibration graph of Metadoxine was obtained by a validated UV spectrophotometric method at 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). A backing membrane of 4% PVA was also coated over one side of all formulations. Physico-chemical 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.

Keywords: Design, In-Vitro Characterization, Metadoxine, Buccal Patches

INTRODUCTION:

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike [1]. Bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [2-4]. The biological surface can be epithelial tissue or it can be the mucous membrane adhere on the surface of a tissue. If adhesion is to a mucous coat, the

phenomenon is referred to as mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application3.Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route drug delivery provides the direct entry to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability [5-7]. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action [8-12].

Metadoxine is a selective antagonist of the serotonin receptor subtype 5-HT2B and displays high affinity to the gamma-aminobutyric acid (GABA) transporter. *In vitro* enzymatic assay revealed that Metadoxine reduced the activity of the GABA transaminase enzyme, responsible for the degradation of GABA. Electrophysiological studies also showed that Metadoxine increased inhibitory GABA based synaptic transmission via a presynaptic effect. As it does not affect dopamine, norepinephrine or serotonin levels, Metadoxine displays a novel mechanism of actionas a monoamine-independent GABA modulator.

The main aim is to formulate the drug Metadoxine buccal patch in a novel dosage form, which is currently unavailable in the market.

MATERIALS

Table-1: List of materials and reagents used in the study

Reagent	Manufacturer
Borassus flabellifer Resin	Natural source
Pectin	Himedia Laboratories, Mumbai
Sodium alginate	S.D Fine Chemicals Ltd., Mumbai
Polyvinyl alcohol (M.W:160000)	Himedia Laboratories, Mumbai
Sucrose	S.D Fine Chemicals Ltd., Mumbai
Vanillin	Himedia Laboratories, Mumbai
Metadoxine	Apotex Research Pvt. Ltd.

PREFORMULATION STUDIES

Preformulation studies are vital for any kind of formulation since they assure the success of the final product both physically and chemically. The important preformulation studies with respect to this work involves:

1. Authentication of source of the Palmyra palm fruit resin
2. Preparation of the *Borassus flabellifer* fruit resin

3. Compatibility studies using FT-IR

4. Preparation of calibration graph of Metadoxine using UV-visiblespectrophotometry

1. Authentication of source of the Palm fruit resin:

Various parts of the Palmyra palm such as fruits (unripened and ripened), leaf with stalk and flower were submitted for identification and authenticationof the botanical source to the Botanical Survey of India, Southern Regional Centre, Coimbatore.

2. Preparation of *B. flabellifer* Fruit Resin (BFR) [25]:

A ripened fruit of *B. flabellifer* was obtained from a local vendor. The black coloured peel of the fruit was removed and the three seeds along with the fibrous pulp was 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 colour.
The seed and fibers were removed by means of filtration using a muslincloth. The filtrate (fruit pulp) was concentrated by evaporating the liquid (at not more than 45°C), till the extract dried into a golden brown coloured sticky resin. The process of drying must be done carefully, since increase in temperature may char the product. The dried resin was stored in an air-tight container at room temperature.

3. Compatibility studies using FT-IR

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. Therefore, in the present work, a study was carried out using infrared spectrophotometer 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.

4. Preparation of calibration graph of Metadoxine using UV-visible spectrophotometry

10mg of Metadoxine was dissolved in PBS pH-6.8 and the volume wasmade up to 100ml with the same, which gives a stock solution of 100µg/ml. From thisstock solution aliquots of 0.4 – 4 ml were withdrawn using a pipette and transferred toa series of ten 10ml standard flasks. The volumes were made up with PBS pH-6.8. Thus, the concentration range of 4–40 µg/ml was obtained. The absorbances 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 meanabsorbance values. A calibration graph of absorbance vs. concentration was plotted.

FORMULATION OF METADOXINE BUCCAL PATCHES

1. 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 volume of plasticizer (PEG-400) and permeation enhancer (DMSO). Finally, 9 polymer ratios using Pectin, Sodium alginate and PVA-160000 were found to be suitable.

2. Formulation of buccal patches by Solvent casting method:

Weighed quantity of BFR was added to distilled water and dissolved using a magnetic stirrer set at 500 rpm to obtain a uniform solution. 12 formulations using Pectin (F1-F3), SA (F4-F6) and PVA (F7-F9) in varying proportions were addedto 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 to 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 patchesform a smooth non-sticky surface.

Table-2: 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

3. 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.

RESULTS & DISCUSSIONS

I. PREFORMULATION

1. 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.

2. Preparation of the *Borassus flabellifer* fruit resin

Fig-1: *B. flabellifer* Fruit Resin

3. Compatibility studies using FT-IR [30]

The physical mixtures of Metadoxine and polymers were subjected to FT-IR analysis to identify any interaction between them.

FT-IR spectra of Metadoxine, BFR, Pectin, Sodium alginate, PVA and mixtures of drug with each excipient are given in Figures 9-7.

4. Preparation of calibration graph of Metadoxine using UV-visiblespectrophotometry

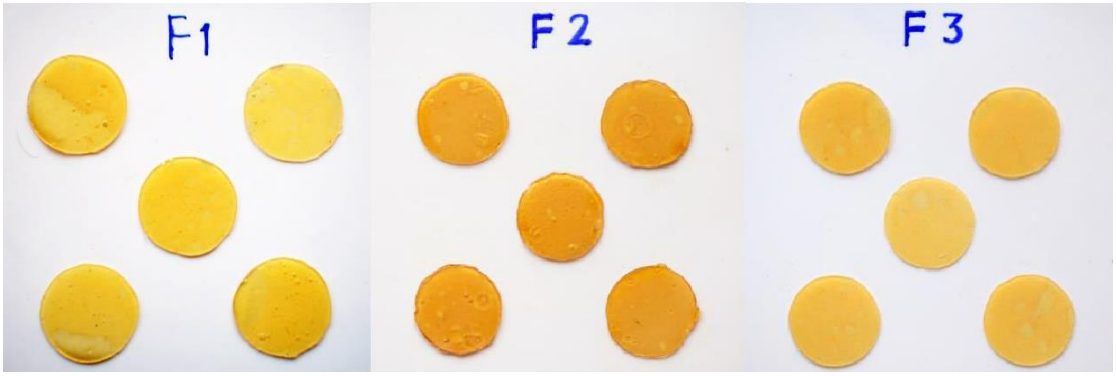
The mean absorbance values for the standard concentrations of Metadoxine are given in the table-. It was found that the concentration of Metadoxinein the range 4-40µg/ml obeyed Beer-Lambert's law. The correlation coefficient was found to be 0.997862.

Table-3: Calibration graph of Metadoxine

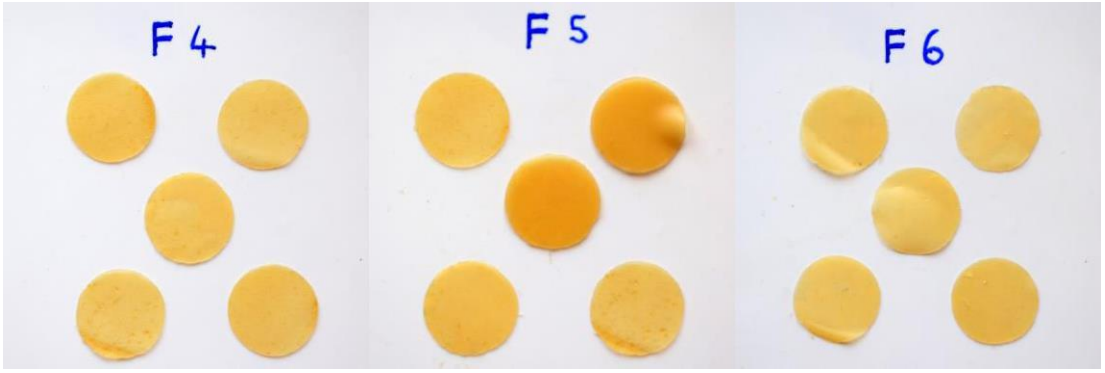
S. no	Concentration (µg/ml)	Absorbance
1	4	0.1587
2	8	0.1954
3	12	0.3350
4	16	0.4220
5	20	0.5418
6	24	0.6303
7	28	0.7253
8	32	0.8514
9	36	0.9826
10	40	1.0630

II. FORMULATION OF METADOXINE BUCCAL PATCHES

1. Formulations F1-F3: combination of BFR + Pectin



2. Formulations F4, F5 & F6: combination of BFR + Sodium alginate



3. Formulations F7, F8 & F9: combination of BFR + PVA

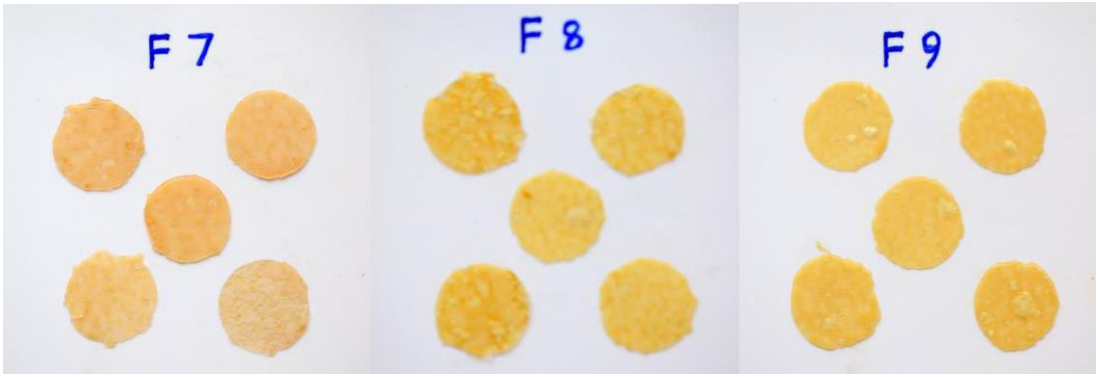


Fig-2: Photographs of Metadoxine buccal patches

III. EVALUATION OF METADOXINE BUCCAL PATCHES

A. Evaluation of physico-chemical properties

The results of physico-chemical evaluation tests such as thickness, weight variation, folding endurance swelling index,surface pH, drug content assay and bioadhesion strength are given as follows:

Table-4: Physico-chemical 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

- 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 isvalid.
- The weighs of the patches of different formulation codes were in the range of 343.4± 4.21 mg to 425.8 ± 3.77 mg, whereas the intra-batch variation is relatively smallerwith a maximum standard deviation of 4.43 mg (F9).
- The patches F7-F9 exhibited remarkable folding endurance with values as high as 256, whereby the lowest value of 16 was observed for F2. Increase in the additionalpolymer (Pectin/SA/PVA) increases the folding endurance,
- Swelling index of all the formulations were 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. A decrease in pH was observed with increase in BFR concentration, which is due to the inherent pH (5.5) of the polymeritself.
- The force required to detach the patch from the animal's tissue is directly proportional to the bioadhesion strength of the patches. In this aspect, the patch withhighest 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 anddose calculation were appropriate and has good reproducibility.

Correlation of coefficient values various kinetic models with respect tothe in-vitro diffusion study were tabulated to determine the best-fit model and the mechanism of diffusion.

In-vitro permeation studies revealed that the formulation F7 (BFR :

PVA- 3:5) exhibits a sustained release of more than 6 hrs and hence PVA is a suitablecombination for BFR for a sustained release drug delivery.

The release kinetic modelling 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 modelling helped to determine the release mechanism of the buccal patch formulations as **'non-Fickian mechanism**' (accordingto Table-4 &20), since the average 'n' exponent value is 0.9752 ± 0.01.

SUMMARY

Natural polymers are trending as a reliable alternative for synthetic andsemi synthetic polymers, in the development of a large number of novel drug delivery systems. One such new alternative to be used as a mucoadhesive polymer- **B. flabelliferFruit resin**, especially for buccal drug delivery was introduced.

The novel polymer, in combination with two other natural polymers (Pectin & Sodium alginate) and one synthetic polymer (PVA), was used to formulate abuccal drug delivery system containing **Metadoxine**. This drug was chosen due to its low half-life (maximum of 60 min) and attempt was made to reduce its dose by sustaining its release. Also alcoholism is a serious social and health issue affecting a significant amount of world population and hence a therapeutic alternative to cure alcoholism is a need of the hour.

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, including BFR. The calibration graph of Metadoxine was obtained by a validatedUV spectrophotometric method at 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). A backing membrane of 4% PVA was also coated over one side of all formulations.

Physico-chemical 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 diffusionstudy was also performed to examine the release pattern of the formulations, which wasextended to determine the kinetics and mechanism of the release.

CONCLUSION

Metadoxine buccal patches were formulated and evaluated successfully by solvent casting method; following standard operating procedures. The evaluation tests revealed that *B. flabellifer* is a suitable polymer for developing a sustained release buccal drug delivery system. Among the developed buccal patches, the formulation F7with 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 sustained release of 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 mucoadhesivepolymer of natural origin.

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