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FORMULATION AND EVALUATION OF BUCCAL PASTE CONTAINING *MELAMPODIUM DIVARICATUM* AGAINST MOUTH ULCER

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ABSTRACT

Buccal formulations is a medicine given between the gum and the inner lining of the mouth cheek. Buccal paste is the medication used for the relief of symptoms of mouth ulcer. *Melampodium* extract usually used to govern several diseases such as dental carries, malaria and possess antileishmanial, antibacterial, anti-inflammatory and antinociceptive activity. *Melampodium* comprises some essential phytoconstituents such as sesquiterpenes, E-caryophyllenes, Germacrene. The plant extract was characterized by decoction process. The present research has been undertaken with the aim to formulate and evaluate the buccal paste containing aqueous extract of flower buds of *Melampodium divaricatum* against mouth ulcer. Paste formulation was designed using accurately weighed amount of drug extract along with other additives such as sodium CMC, starch, methyl paraben, propyl paraben, white soft paraffin etc. Formulations were evaluated for following parameters such as pH, spreadability, homogeneity, viscosity, extrudability, anti –bacterial activity and in-vitro drug release. The formulation was finalized through optimization by central composite design. The result showed that the optimized herbal oral formulation containing *Melampodium divaricatum* extract shows that all physicochemical parameters were found to be compactable with the normal range. Anti-bacterial study of formulation revealed excellent efficacy against mouth ulcer. Herbal buccal paste was formulated which was stable and effective for the treatment of mouth ulcer.

KEYWORDS: *Melampodium divaricatum, buccal paste, mouth ulcer.*

INTRODUCTION

Herbal medicines are referred to the use any part of the plant for healing and treating diseases purposes. Herbal medicines have been used widely throughout human history and according to world health organization (WHO) about 80% of human population used herbal medicines for primary health care. In addition, more than, more than 35,000 plant species have been reported to be used in various human cultures around the world for medical purposes. Some of them are potent antimicrobial, antidiabetic, antiviral, anticancer, and antifungal.[1] Although herbal medicines have benefits to increased, their safety, efficiency, quality, and importance of industrialized and developing countries. Herbal medicines are getting increasing patient compliance as they are avoiding typical side effects of allopathic medicines.1.42 billion people, are dependent on traditional medicines for the treatment of various diseases. Medicinal plants have been a major source of cure for human diseases since time immemorial.[2]

Buccal drug delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration. Administration of dosage forms through the oral route is most convenient and suitable route. Some classes of patients are facing difficulty to take oral formulations i.e. geriatric, pediatric, dysphagia patients due to difficulty of swallowing or chewing dosage forms.[3] Buccal drug delivery provides site-specific release of the drug on the mucosa and involves drug absorption through the mucosal barrier to reach the systemic circulation. Since the drug content within the buccal formulations can be considerably lower than that of tablets and capsules, toxicity or undesired side effects will potentially be significantly reduced.[4]

Ulcers are lesions on the surface of the skin or mucous membrane characterized by a superficial loss of tissue. Mouth ulcer in which sores are appear on any of soft tissues of the mouth. Buccal delivery mainly achieved through the mucoadhesive dosage forms it offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility.[2] Mucosal delivery of drugs *via* the buccal route is still very challenging in spite of extensive

clinical studies. Oral mucosal ulceration is a common condition with up to 50% of healthy adults suffering from recurrent minor mouth ulcers (aphthous stomatitis). Evaluated the efficacy and tolerability of a mucoadhesive paste compared with a pain-relieving oral solution for the treatment of aphthous stomatitis. The mucoadhesive paste was found to be more effective than the oral solution in terms of healing time and pain intensity after 12 and 24 h. Local adverse effects 1 h after the treatment were significantly less frequent among the mucoadhesive paste patients compared with the oral solution patients. Buccal delivery provides advantages such as ease of administration, ease of Termination of therapy, permits localization of drug to the oral cavity for a prolonged period of time, can be administered to unconscious patients, offers a passive system of drug absorption, and does not require any activation. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The paste is a pharmaceutical dosage form. It consists of a fatty base and at least 25% of a solid substance. It provides relief from swelling and redness in the affected area. Treats and relieves discomfort caused by mouth sores. It works by decreasing inflammation in the mouth. Buccal paste is given between the gum and the inner lining of the mouth. This area called the buccal pouch. The drug delivery system targeting the oral mucosa face a major challenge, especially the short residence time in the mouth due to the "saliva wash out".[4]

The present study aims to formulate and evaluate buccal paste containing aqueous extract of flower buds of *Melampodium divaricatum* against mouth ulcer. *Melampodium divaricatum*, commonly called Melampodium or butter daisy, is an aster family annual that produces solitary daisy-like flowers (to 1" wide) with yellow rays and darker yellow centers from spring to fall on plants growing 12-24" tall. As the flowers fade, the stems branch to produce additional bloom. Light green, entire, oblong stem leaves on purplish stems. Easily grown in average, evenly moist, well-drained soils in full sun. Needs consistent moisture, but prefers soils slightly on the dry side. Sow seed directly in the garden after last frost date. For earlier bloom, start seed indoors 6-8 weeks before last frost date. Set seedlings or purchased plants out after last frost date. Although plants are quite tolerant of hot and humid summer weather, taller stems tend to flop in the heat of summer. Deadheading is not required. May self-seed in optimum growing conditions. Plant mainly active against oral pathogens and possess anti-inflammatory activity.[2]

1. MATERIAL AND METHODS

1.1 Materials

Flower buds of *Melampodium divaricatum* collected from local area of payangadi. All other excipients and chemicals used were of analytical reagent grade.

1.2 Instruments used

Double beam UV spectrometer, FTIR (Bruker Alpha-Attenuated Total Reflectance FTIR), Digital pH meter(Roy Instruments Varanasi), Brookfield viscometer(LVDV Prime-1).

1.3 Extraction of *Melampodium divaricatum*

Extraction carried out through the process of decoction. Decoction involves first drying the plant material; then washing, slicing, or cutting the material to allow for maximum dissolution. Then the sample was soaked with 100 ml of ethyl acetate for 2 days. Which enhances the process of extraction. It was then filtered using what's man filter paper.[5]

1.4 Preformulation study

1.4.1 Organoleptic evaluation

Drug was tested for colour, odour, and taste.

1.4.2 Phytochemical tests for Melampodium extract

The extract was tested for active chemical constituent, mainly for terpenoids.

1.4.3 Determination of absorbance maxima

Dissolve accurately weighed 100 mg of powdered extract in phosphate buffer. Make up to 100 ml in a volumetric flask using phosphate buffer. Then it filtered through what's man filter paper. Then 1 ml pipetted out and diluted with 100 ml methanol solution to get 10 µg/ml. the absorption maxima of standard solution determined by scanning the resulting stock solution in UV spectrometer at 200-400 nm.[3]

1.4.4 Preparation of standard calibration curve

A spectrometric method based on the measurement of absorbance at 220 nm. The stock solution was freshly prepared by dissolving 100 mg of powdered extract in 10 ml of methanol in a 100 ml volumetric flask and then making up the solution up to the mark using buffer solution. This is considered as standard solution. From this stock 0.1, 0.5, 1, 1.5, 2.0, 3.0, and 3.5 ml were taken separately and made up to 10 ml with distilled water to produce 10, 50, 100, 150, 200, 300 and 350 µg/ml respectively. The absorbance was measured at 220 nm using UV Visible spectrophotometer against phosphate buffer as blank and a calibration curve was plotted by taking concentration on x- axis and absorbance on y-axis.[6]

1.4.5 Solubility of drug

Solubility test was conducted to determine the dissolution medium and other solvents. Solubility of drug was observed in different solvent such as distilled water, phosphate buffer (pH 6.8), ethyl acetate, chloroform.[4]

1.4.6. Drug-excipients Compatability

FTIR spectroscopy method was used for carried out drug-excipient compatibility study. FT-IR spectra of pure drug, sodium CMC, starch, white soft paraffin, and their

physical mixtures were taken by KBr pellet technique between 400–4000cm^{-1}. Once spectra were recorded, the peaks of pure drug, polymers and physical mixtures of polymers and drug were compared for incompatibility.[7]

1.4.7. GC/MS analysis

The qualitative and quantitative analysis of extraction was carried out using Perkin Elmer Clarus 680GC/600C mass selective detector (MSD) system. Fused silica HP-5MS column cross-linked with 5% phenylmethyl siloxane of 60 m length and internal diameter of 0.25 mm was used. The initial oven temperature was 50°C for 2 min and then ramp at 5°C min^{-1} up to 260°C.Injector and transfer line temperature was 250 °C and 200°C respectively. The holding time was 2 min and the solvent delay time was 8 min. Helium was used as a carrier gas at 1 mlmin^{-1}. 2 µl volume of sample was injected. Split ratio 50:1 and scan range of 50–600 Da was used. The identification of constituents was done on the basis of their retention time and mass spectra library search (NIST).[7]

1.5. Method of preparation of buccal paste

Weigh the required amount of herbal drug and excipients. Ingredients are completely triturated with half of the base. Remaining amount of base are added and formulate the paste by the fusion method.[1]

Table 1: Formulation table.

Formulations	Extract (g)	Sodium CMC (g)	Starch (g)	Methyl paraben (g)	Propyl paraben (g)	White soft paraffin (g)
F1	0.3	0.75	2.5	0.01	0.03	6.41
F2	0.3	1	2.5	0.01	0.03	6.16
F3	0.3	0.5	2.5	0.01	0.03	6.66
F4	0.3	1	1	0.01	0.03	7.61
F5	0.3	0.5	1	0.01	0.03	8.16
F6	0.3	0.75	1	0.01	0.03	7.94
F7	0.3	0.5	4	0.01	0.03	5.16
F8	0.3	1	4	0.01	0.03	4.66
F9	0.3	0.75	4	0.01	0.03	4.91

1.6. Design of experiment (DOE)

Response surface methodology (RSM) is a mathematical and statistical technique useful for modelling and analysing the effect of several quantitative variables in the response of interest. This methodology saves time and effort by reducing the number of experimental runs and gives optimized and statistically significant results. Hence it is widely used in various fields of engineering and applied sciences to optimize the process variables. The most common experimental design used are Central Composite Design (CCD), Box-Behnken (BBD) and Boehlert design.

Central composite design using Design-expert software® version 7.0.0 was employed to evaluate the independent and interaction effects of process parameters such as viscosity, invitro-drug release. Preliminary experiments were performed to determine and define the levels of an independent factor. A two level-factor design was employed. Considering 2central points, total of 13 experimental runs were generated.[7]

1.7. Evaluation of buccal paste

1.7.1. Physical evaluation

Physical parameters such as colour, odour, and consistency were checked visually.

Colour: The colour of formulations was checked by visual inspection.

Consistency: The consistency of the formulations was checked by applying on skin.

Odour: The odour of the formulations was checked by mixing the gel in water and observing the smell.

1.7.2. Homogeneity

All prepared formulations were tested for homogeneity by visual inspection after the paste have been set in to the container. They were tested for their presence and appearance of any aggregates.[10]

1.7.3. Viscosity

Viscosity were determined using Brookfield viscometer. Paste were tested for their rheological characteristics at 250C using Brookfield viscometer (DV-3 Programmable rheometer). The measurement was made over the whole range of speed setting from 10 rpm to100 rpm with 30 seconds between 2 successive speeds and then in a descending order.[8]

1.7.4. Extrudability

The formulated paste were filled in standard capped collapsible aluminium tubes and sealed by crimping to

the end. The weight of filled tubes were recorded and the tubes were sandwiched between two glass slides and were clamped. 500gm weight was placed over the slides and then the cap was removed to extrude. The amount of extruded paste was collected and weighed. Extrudability was determined by calculating the percentage of extruded paste.

When it is greater than 90% then extrudability is excellent.

When it is greater than 80% then extrudability is good

When it is 70% then extrudability is fair.

1.7.5. pH

The pH of paste formulations were determined by using digital pH meter. Take 1 gm of paste and dissolved in 10 ml of distilled water and keep apart for two hours. Then the measurement of pH of formulation was done by dipping the glass electrode completely into the paste system three times and the average values are reported.[9]

1.7.6. Spreadability

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from paste that is placed in between the slides under the direction of certain load. If the time taken for separation of two slides is less then better the spreadability. Spreadability is calculated by using the formula.[9]

$S = M \times L / T$

Where M = weight to upper slide

L = length of glass slides

T = time taken to separate the slides

1.7.7. Invitro-drug release study

invitro-drug release study mainly carried out through invitro diffusion study, here egg membrane was used.2 g of paste were placed in donor compartment of cell. The surface of membrane was in contact with the receptor compartment containing 150 ml of phosphate buffer of pH6.8. The receptor compartment was continuously stirred. the study was carried out for 6hr. The surface area available for diffusion was calculated. The sample was withdrawn at predetermined interval and same volume was replaced with fresh phosphate buffer. The absorbance of withdraw sample was measured after suitable dilution at respective ƛ max to estimate drug concentration. the experiment was carried out in triplicate and average values are reported.[10]

1.7.8. Anti-bacterial activity

The antibacterial activity of optimized formulation and blank formulation were carried out by agar-plate method The antibacterial test was performed by using *E .coli*. Prepared nutrient brought and poured in to sterile petri plates and kept aside for drying and cooling. After that *coli* culture were spread by micron wire loop. A sterile cork borer 6 mm diameter was used to drill holes 4 mm deep. Then place 0.5 gm of paste in to these holes. Plates were then incubated at 27°C for 48 hr. Then the zone of inhibition (diameter in mm) was measured.[11]

1.7.9. Stability study

Stability studies were performed to observe the effect of environmental condition or storage condition on formulation. The optimized formulation was kept in accelerated stability condition at 25°C temperature 60 ± 5% relative humidity, 30°C temperature 65 ± 5% relative humidity and 40°C temperature 75 ± 5% for a period 3 months as per ICH guidelines. The placed sample was withdrawn at 1-, 2- and 3-months interval and evaluation was carried out for physical appearance, pH, viscosity, spreadability, extrudability.[12]

1.8. RESULT AND DISCUSSION

1.8.1. Organoleptic evaluation

Table 2: organoleptic evaluation of Extract.

Description	Liquid
Colour	Brown
Odour	Charecteristic odour
Taste	Slightly bitter

Extract appears as brown colour liquid with characteristic odour and slight bitter taste.

1.8.3. Phytochemical tests for Melampodium extract

Table 3: Phytochemical Tests of Melampodium Extract.

PROCEDURE	OBSERVATION	INFERENCE
Salkowski's test	Reddish brown colour	Presence of terpenoids
Sulphur powdered test	Sulphur sinks down the mixture	Presence of terpenoids
Trichloroacetic acid test	Coloured precipitate	Presence of terpenoids

Fig.1: Phytochemical Tests of Melampodium Extract.

1.8.4. Determination of absorbance maxima

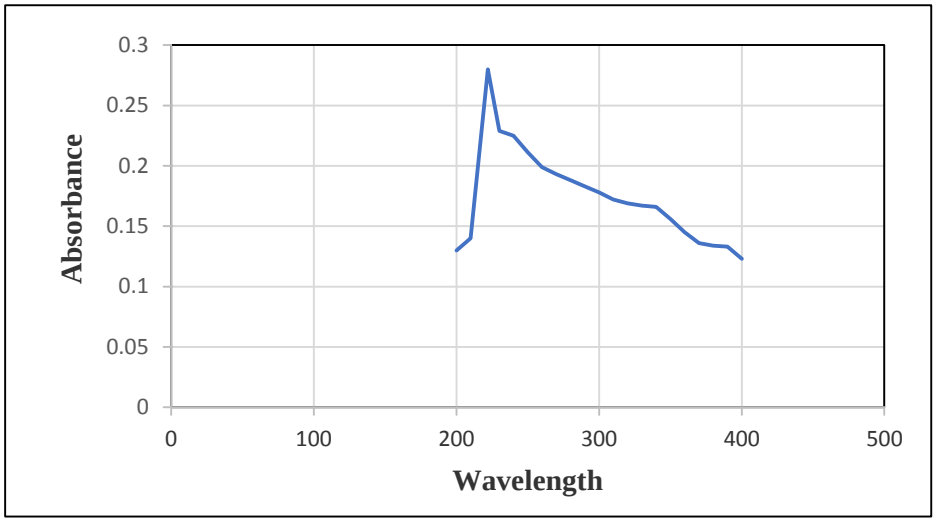
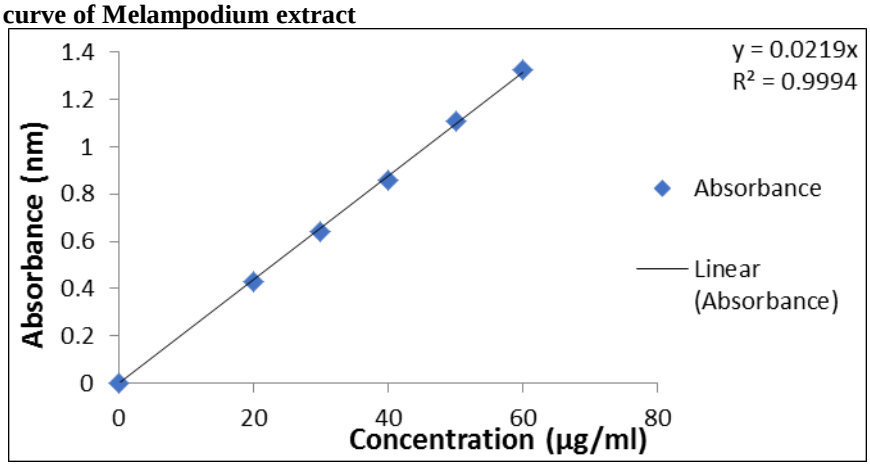


Fig.2: UV spectrum of Melampodium extract in phosphate buffer pH6.8.

The Melampodium extract was scanned by UV spectroscopy and λ max was found to be 220nm.

1.8.5. Calibration curve of Melampodium extract



All values are expressed as a mean of ± SD, n=3

Fig 3: Standard calibration curve of Melampodium extract in phosphate buffer pH6.8 at 220nm.

The Melampodium extract was scanned in UV region (200-400nm) to find out the wavelength of maximum absorption (λ max). The λ max was found to be at 220nm. So the calibration curve of Melampodium extract was plotted at this wavelength. Standard calibration curve of Melampodium extract was determined in phosphate buffer pH6.8 by plotting absorbance against concentration at 220nm. The calculation of drug content *in-vitro* release and stability studies are based on this calibration curve.

1.8.6. Solubility of drug

Solubility extract in various solvent were carried out as shown in table.

Table 4: Solubility of Melampodium extract.

NAME OF THE MEDIA	SATURATION SOLUBILITY OF DRUG
Distilled water	Soluble
pH 7.4 phosphate buffer	Soluble
pH 6.8 phosphate buffer	Soluble
Ethyl acetate	Freely soluble
Chloroform	Slightly Soluble

1.8.7. Drug- excipient compatibility

FT-IR studies were conducted in Melampodium extract, sodium CMC, starch, white soft paraffin . The FT-IR spectrum is shown below.

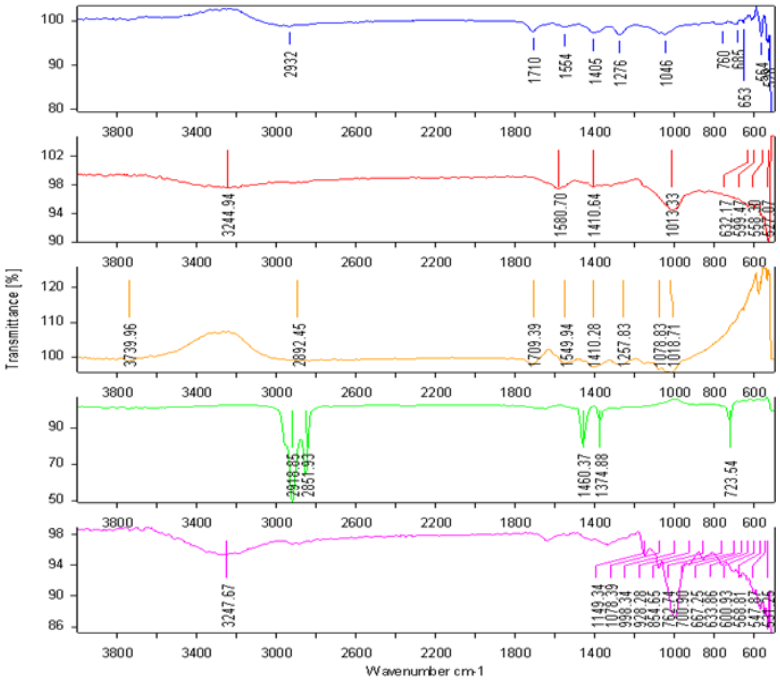


Fig 4: FT-IR of Melampodium extract, sodium CMC, white soft paraffin, starch.

During FT-IR, there is no significant change in the peak in the FT-IR spectrum of extract with sodium CMC, starch, white soft paraffin. It indicates that there is no chemical interaction between the drug and other components of paste. This shows that the Melampodium extract is compatible with other excipients.

1.8.8. GC/MS analysis

Table 5: chemical composition of Melampodium identified using GC/MS

Retention time (min)	Compound name	Abundance %
26.71	E-Caryophyllene	55.24
28.91	Germacrene D	13.41
28.96	Bicyclogermacrene	9.21
29.82	Geraniol	17.08
34.14	β-Elemene	0.37
35.35	Patchoulane	0.08
35.59	Linalool	0.21
37.55	Cadinene	0.22
38.35	Germacrene A	0.82
39.34	Germacrene D-4-ol	1.22
30.28	3-Hydroxy-5-isopropyl-2-methylbenzo-1,4-quinone	0.05
Percentage of total compounds identified		99.21
Other trace compounds		0.79

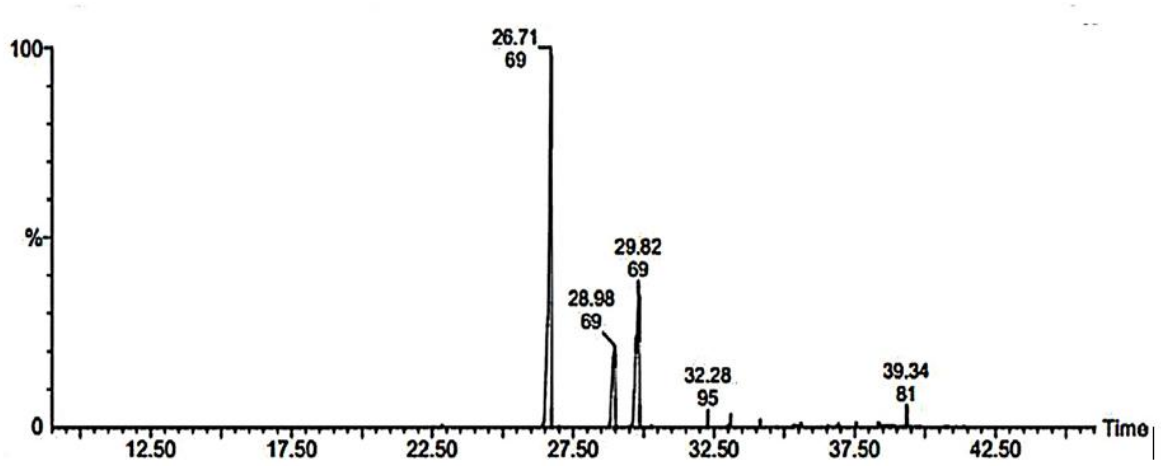


Fig.5: GC/MS chromatogram of melampodium.

Different peak indicates the presence of E-Caryophyllene, Germacrene D, Bicyclogermacrene, Geraniol, β-Elemene, Patchoulane, Germacrene A etc. These compositional analysis indicate that, extract possess high yield of sesquiterpene.

1.8.9. Design of experiment (DOE)

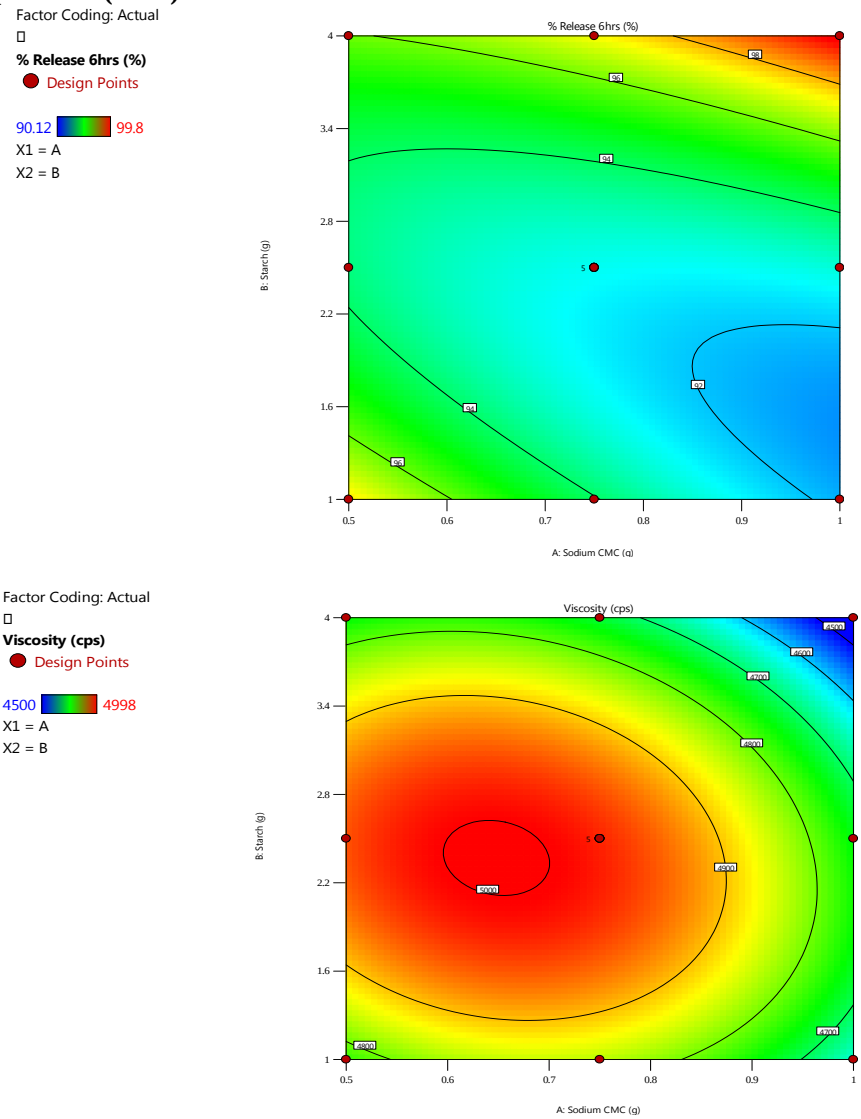


Fig. 5: counter plot showing the effect of sodium CMC and starch on (a)percentage release and (b) viscosity.

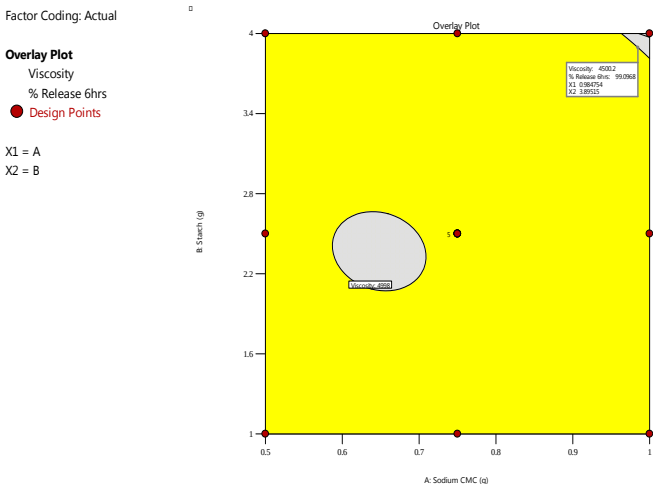


Fig. 6: overlay plot.

Optimization was done by design expert software. Two factor were selected for optimizing the formulation. The factor selected were starch and sodium CMC. Central composite design was used for optimization. To determine the best formulation, two response i.e., viscosity and in-vitro release were considered.13 formulations were suggested by the software. After analysis optimized data F4 was selected as the optimized formulation having highest in vitro drug release and lowest viscosity. Hence F4 was selected as optimized formulation.

1.9. Evaluation of buccal paste

1.9.1. Physical evaluation

Table 6: Physical Evaluation of Formulations.

FORMULATIONS	COLOUR	CONSISTENCY	ODOUR
F1	Yellowish brown	Good	Charecteristic
F2	Yellowish brown	Good	Charecteristic
F3	Yellowish brown	Good	Charecteristic
F4	Yellowish brown	Good	Charecteristic
F5	Yellowish brown	Good	Charecteristic
F6	Yellowish brown	Good	Charecteristic
F7	Yellowish brown	Good	Charecteristic
F8	Yellowish brown	Good	Charecteristic
F9	Yellowish brown	Good	Charecteristic

1.9.2. Homogeneity

Table 7: Homogeneity of formulations F1-F9.

FORMULATIONS	HOMOGENEITY
F1	GOOD
F2	GOOD
F3	GOOD
F4	GOOD
F5	GOOD
F6	GOOD
F7	GOOD
F8	GOOD
F9	GOOD

It was found to be homogenous and no phase separation was found.

1.9.3. Viscosity

Rheological studies were conducted on formulations.

Table 8: viscosity of formulations F1-F9.

FORMULATION CODE	VISCOSITY
F1	4998±4.35
F2	4636±7.54
F3	4682±2.51
F4	4500±1.01
F5	4798±4.04
F6	4754±2.64
F7	4931±3.0
F8	4852±1.52
F9	4625±4.50

The rheological behaviour of all formulated paste were studied using Brookfield viscometer at rpm 50 and spindle no.63 was used. The viscosity of the paste formulation were found to be in the range in between 4500-5000Cps.

1.9.4. Extrudability

Table 9: Extrudability of formulations F1-F9.

FORMULATIONS	EXTRUDABILITY (%)
F1	78
F2	79
F3	77.5
F4	89.5
F5	89
F6	78.96
F7	77.5
F8	88.98
F9	88.23

1.9.5. pH

Table 10: pH of formulations F1-F9.

Formulations	pH
F1	6.6±0.058
F2	6.5±0.176
F3	6.8±0.235
F4	6.8±0.235
F5	6.6±0.96
F6	6.8±0.36
F7	6.7±0.75
F8	6.8±0.53
F9	6.3±0.19

The pH values of all the prepared formulation ranged between 6-7 which lies within normal pH range of buccal cavity.

1.9.6. Spreadability

The spreadability of formulations were studied using apparatus fabricated in our laboratory.

Table 11: Spreadability of formulation F1-F9.

FORMULATIONS	SPREADABILITY(CM/S)
F1	3.5
F2	3
F3	3.5
F4	3.6
F5	3.4
F6	3
F7	3.4
F8	3.3
F9	3.3

Spreadability of formulations were in range of 3-3.6g.cm/sec.

1.9.7. Invitro-drug release study

In vitro drug release of formulations were determined using Franz-diffusion cell fabricated in our laboratory and the results are given below.

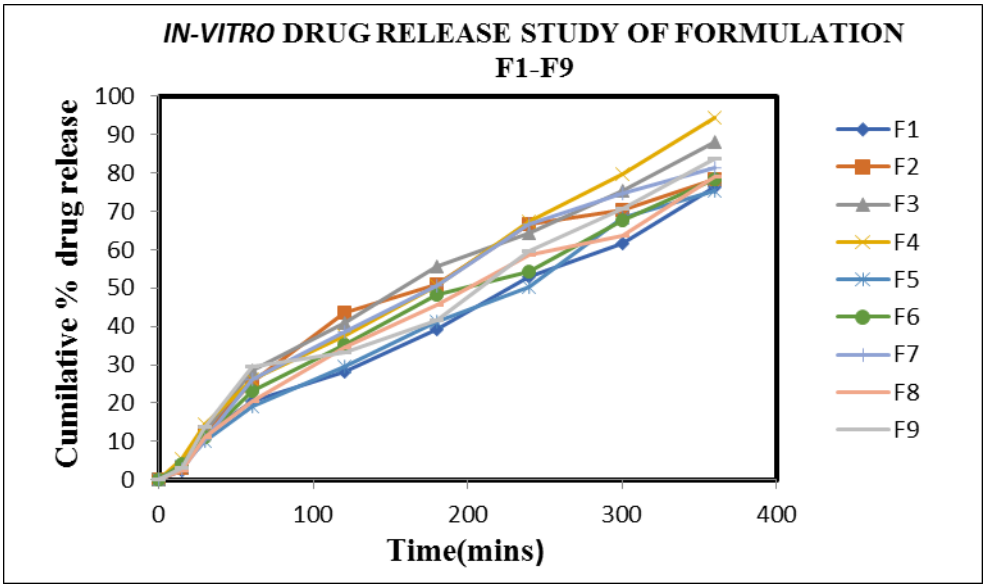


Fig.7: cumulative percentage of drug release of formulation F1-F9.

The in-vitro drug release of all the 9 formulations were determined using franz-diffusion cell. Among all the formulations F4 showed greater in-vitro drug release than all other formulation.

1.9.8. Anti-bacterial activity

The microbial study was done on the optimized formulation and zone of inhibition was measured.

Table 12: Microbial study of optimized formulation.

Formulations	Zone of inhibition(mm)
F4 formulation	22
Standard	19
Blank	14

Fig.8: Microbial study of optimized formulation.

1.9.7. Stability study

From in-vitro release studies of prepared formulations, F4 showed the best drug release profile. Hence it was used for stability studies.

Table 13: stability study at 25°C temperature 60%±5%RH.

Evaluation parameter	F4	F4	F4
	Month 1	Month 2	Month 3
Colour	Yellowish brown	Yellowish brown	Yellowish brown
H	6.8	6.8	6.8
Viscosity	4500	4500	4500
Spreadability	33.18	33.18	33.17
Extrudability	89.4	89.5	89.4

Table 14: stability study at 30°C temperature 65%±5%RH.

Evaluation parameters	F4	F4	F4
	Month 1	Month 2	Month 3
Colour	Yellowish brown	Yellowish brown	Yellowish brown
Ph	6.8	6.8	6.8
Viscosity	4500	4500	4500
Spreadability	33.19	33.18	33.17
Extrudability	89.4	89.5	89.4

Table 15: stability study at 40°C temperature 75%±5%.

Evaluation parameters	F4	F4	F4
	Month 1	Month 2	Month 3
Colour	Yellowish brown	Yellowish brown	Yellowish brown
pH	6.8	6.8	6.8
Viscosity	4500	4500	4500
Spreadability	33.19	33.18	33.17
Extrudability	89.4	89.5	89.4

From the 9 formulations, the optimized formulation F4 was used for stability studies as per ICH Guidelines for 3 months. It showed that the prepared Paste passed stability studies with no much significant changes in physical appearance.

CONCLUSION

Buccal paste containing aqueous extract Melampodium divaricatum formulated they were within acceptable limits for various physicochemical evaluations. It can be concluded that buccal paste containing extract of melampodium divaricatum were safe, stable and good for mouth ulcer treatment From the above results it is clearly show that all the prepared formulation was yellowish green in colour and having good homogeneity and p H of all the formulation was in the range compactable with normal p H range of oral cavity.

Natural remedies are more acceptable in the belief that they are safer with lesser side effects than the synthetic medicines. Rheological behaviors of formulations were studied with Brookfield viscometer which indicated that the viscosity of formulations neither too thick nor too thin. Thus overall the formulations F4 complies with the all parameters of ideal range. And f4 show better antibacterial activity. Accelerated stability studies indicated that the physical appearance, rheological properties , extrudability, spreadability in the optimized formulation remain unchanged upon 3 months. F4 formulation shows the maximum drug release.

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