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FORMULATION AND EVALUATION OF MODAFINIL LOADED MOUTH DISSOLVING FILMS FOR THE TREATMENT OF NARCOLEPSY

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Abstract:

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness, sudden loss of muscle tone (cataplexy), sleep paralysis, and hallucinations during sleep. Modafinil, a wakefulness-promoting agent, is commonly used for the treatment of narcolepsy due to its ability to improve wakefulness and reduce excessive daytime sleepiness. However, conventional oral dosage forms of Modafinil may pose challenges in administration, especially for patients with difficulty swallowing. Mouth dissolving films (MDFs) offer a patient-friendly alternative for drug delivery, providing rapid disintegration and dissolution in the oral cavity without the need for water. This review aims to explore the formulation and evaluation of Modafinil-loaded MDFs for the treatment of narcolepsy, focusing on recent advancements in formulation techniques, excipient selection, and evaluation parameters.

Keywords: Evaluation, Formulation, Modafinil, Mouth dissolving films, and Narcolepsy.

1. Introduction

Due to patient acceptability, medical professionals and manufacturers have traditionally favoured the oral route of administration over the other routes, which include parenteral, topical, rectal, and vaginal. The patient population has found this approach to be popular due to its cost-effectiveness, ease of administration, and convenience [1]. Because of its particular environment, the mouth cavity may be used as a medication delivery site. The oral solid drug delivery system has advanced significantly, moving from traditional dose forms like tablets and capsules to modified release dosage forms and, most recently, fast-dissolving dosage forms (Fig. 1). The development of mouth dissolving medication delivery systems has been driven by the constraint of difficulties ingesting oral solid dose forms [2].

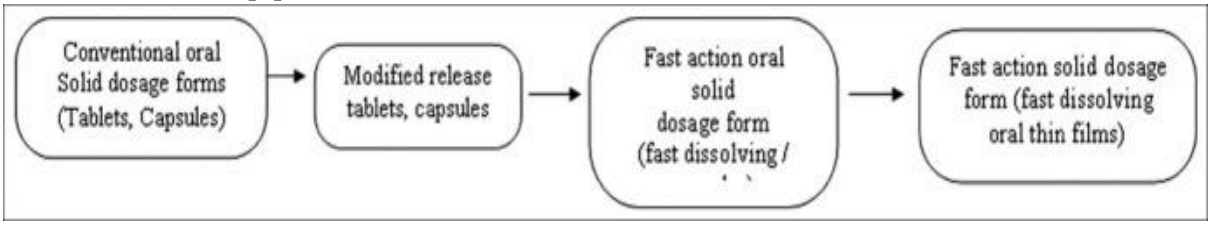

Figure 1 Stages in the Development of Oral Dosage Forms

Oral solid dose forms known as "mouth dissolving films" dissolve and disintegrate when placed in the mouth without the need for water. Mouth dissolving films are becoming more and more

accepted by patients with dysphagia, the elderly, and children who are afraid of choking. Bypassing the first pass metabolism and entering the systemic circulation through the oral mucosa, mouth dissolving films offer convenience, simplicity of administration, and a quicker beginning of action [3].

1.1.Advantages of Mouth dissolving films [4]

The following characteristics make mouth dissolving films superior to traditional oral dose forms:

- They are thin and elegant in appearance.
- Can be available in various shapes and sizes.
- Can be taken without water so beneficial while travelling.
- Disintegrates and dissolves in mouth when placed on tongue so no risk of choking.
- Convenient and accurate dosing in comparison to liquid orals.
- Can be used for site specific local action in the oral cavity.
- Ease of administration to patients of all age group.

1.2.Disadvantages of Mouth dissolving films [4]

With the special feature that makes mouth dissolving film acceptable it suffers from a few limitations as well, as given below:

- High dose of the drug cannot be incorporated into the film
- Taste masking is essential if the drug is having a bitter taste
- Packaging needs special care and equipment's
- The technical challenges in manufacture of films include achieving dose uniformity and uniformity in thickness of mouth dissolving film while casting of the film.

2. Materials And Methods

2.1 List of Materials and Instruments used in the Study

Sr.No	Name	Source
1	Modafinil	CadilaHealthcareLtdGoa
2	DoxylamineSuccinate	IndocoRemediesPvtLtdGoa
3	PyridoxineHydrochloride	MerckIndiaPvt Ltd
4	Hypromellose(HPMC) METHOCEL^{TM}E3Premium	ColorconAsiaPvtLtdGoa
5	Hypromellose(HPMC) METHOCEL^{TM}E5Premium	ColorconAsiaPvtLtdGoa
6	Hypromellose(HPMC) METHOCEL^{TM}E15Premium	ColorconAsiaPvtLtdGoa
7	RaspberrySyrup	SDFine Chemicals
8	Sucralose	JKSucralosePvtLtdDelhi
9	Aspartame	OzoneInternational
10	PolyethyleneGlycol (PEG)400	Himedia
11	CitricAcid	SDFineChemicalsMumbai
12	AscorbicAcid	AvraSynthesisHyderabad
13	MethylParaben	OzoneInternational

14	Honey	DaburIndia
15	PropyleneGlycol	SDFineChemicalsMumbai
16	Ethanol	SDFineChemicalsMumbai
17	SodiumHydroxide	SDFineChemicalsMumbai
18	Glycerin	SDFineChemicalsMumbai
19	SodiumChloride	SDFineChemicalsMumbai
20	Potassiumphosphatemonobasic	SDFineChemicalsMumbai
21	Sodiumphosphatedibasic	Fisherscientific,Mumbai

Table1Materialsusedinthe Study

Sr.No	**Instruments**	**Manufacturer/Supplier**
1	SartoriusElectronicbalance	Shimadzu,Kyoto,Japan
2	DigitalpHmeterLI612	ElicoLI612,Mumbai India
3	UV-VisDoublebeamSpectrophotometer(UV1800)	Shimadzu,Kyoto,Japan
4	MagneticStirrer	RemiEquipmentMumbaiIndia
5	DigitalVernierCaliper(0.01mmLeastCount)	BlissClassic,Bangalore,India
6	DissolutiontestApparatus(VDA8DR)	VeegoInstruments,MumbaiIndia
7	HotAir Oven	TempoInstrumentPvtLtd.,Mumbai, India
8	FTIR:Prestige-IR21	Shimadzu,Kyoto,Japan
9	DifferentialScanningCalorimetryDSCQ20	TAInstruments,Inc;NewCastle,DE,USA
10	ScanningElectronMicroscopyJFC1600	JeolLtd,Tokyo,Japan
11	Tensilestrengthtester	LamiCoatEquipments,Mumbai,India
12	GasChromatography-HeadSpace syste with Flame Ionization m Detector(HSGC)-Clarus500(GC-FID)	PerkinElmerClarus500(GCFID)
13	Stabilitycontroloven	PatelScientificInstruments Pvt Ltd, AhmedabadGujarat

Table2Instrumentsusedinthe Study

2.2 FormulationDevelopmentandOptimizationofModafinilMouthDissolvingFilms[5]

2.2.1. MethodofAnalysis

- **PreparationofReagents and Solutions**
  - Makinga Solution of0.2 MSodium Hydroxide
  - Tomakeasolutionofsodiumhydroxide(0.2M).Wepreciselyweighed8 g of sodium hydroxide and diluted it to make 1000 ml.
  - MakingaPotassiumDihydrogen PhosphateSolution,0.2 M
  - 27.22 g of potassium dihydrogen phosphate were precisely weighed and diluted with filtered water to a volume of 1000 ml in order to create 0.2 M potassium dihydrogen phosphate

solution.

- pH6.8PhosphateBuffer Preparation
- Asolution of potassium dihydrogen phosphate (0.2 M) in 50 millilitres was producedtoprovide1litreofphosphatebufferpH6.8.Afteradding22.4ml ofa0.2 M sodium hydroxidesolution, filtered waterwas added to bringthe level up to 1000 ml.

- **Spectrophotometric Method Development for Estimation ofModafinil[6]:** The currentstudyusedaUV-Visiblespectrophotometer(UV1800ShimadzuCo;Japan) to quantitatively analyse modafinil. A standard calibration curve and absorption maxima (λmax) for modafinil were constructed using phosphate buffer at a pH of 6.8.
- A1MeasurementofModafinil'sλmaxinPhosphateBufferatpH6.8Weigh100mg ofmodafinilprecisely,thentransferthecontentstoa100mlvolumetricflask.After that, dissolve in pH 6.8 phosphate buffer and add enough volume to reach 100 ml, yielding a 1 mg/ml concentration. Next, move 10 ml of this solution, or 10 mg/10 ml, into a 100 ml volumetric flask and dilute it to 100 ml, or 0.1 mg/ml, to create a stock solution of 100 µg/ml. In order to ascertain the wavelength of maximal absorbance, a 10 ppm solution was then generated using this stock solution and scanned across aspectrumwavelength range of200nmto400nmusingphosphate bufferpH6.8asablankusingaUVdoublebeamspectrophotometer(ShimadzuUV 1800).A dilution for the calibration curve was also prepared using this stock solution.
- A2: Modafinil Calibration Curve PreparationIn phosphate buffer pH 6.8, several dilutions of 2, 4, 6, 8, 10, 12, 16, 20, and 22µg/ml were prepared using the stock solutionmentionedabove.Theabsorbancesofthedilutionsarethenmeasuredatthe λmax using a UV spectrophotometer with phosphate buffer pH 6.8 serving as the blanksolution.Theexperimentwasconductedintriplicate,andthecalibrationcurve fortherelationshipbetweenconcentrationinµg/mlandabsorbanceatλmax,aswell as the equation for the line of best fit, were produced by calculating the average absorbance value and standard deviation.

2.2.2. DrugandExcipientCompatibilityStudy[7]

The compatibility of the drug and formulation excipients is an important prerequisiteforformulation.Itisthereforenecessarytoconfirmthatthedrugdoes not react with the excipients under experimental condition, which can affect the shelf life of the product and /or can have any untoward effect on the formulation. The compatibility of the formulation is studied using Differential Scanning Calorimetry (DSC) and Fourier transform Infra-red Spectroscopy (FTIR).

2.2.2.1. Drug and Excipient Compatibility Study using DSC for Modafinil Formulation: The formulation of modafinil MDF in a dry state underwent a drug excipient compatibility evaluation using DSC. Ashian Laboratories in Mumbai used the Universal V4SA TA Differential Scanning Calorimetry Instrument for the investigation. Drug-alone and drug-with-polymer thermograms were taken in a nitrogen environment at a scanning rate of one degreeCelsiusperminutethroughoutatemperaturerangeof-100to400degrees Celsius.Weexaminedtherecordedthermogramstolookforanyoddchangesin peak position or appearance.

2.2.2.2. Drug Excipient Compatibility Study using FTIR Spectroscopy for Modafinil Formulation: Using agate, mixes of the pure drug and potassium bromide in a 1:20 ratio were created to evaluate the drug and excipient compatibility, as well as the formulation in its drystate and potassium bromide in the same ratio.Then, using an IR pellet maker, pellets were made from each ofthesemixes.Subsequently,theproducedpelletwasscannedwithinthe4000- 400 cm-1 spectrum. We examined the spectra of the pure medication and the formulation to look for any odd shifts or peak appearances.

2.2.2.3.Formulation of Modafinil[8]

- PreliminaryScreeningforPlacebo films

- **Step1SelectionofProcedureforFilmPreparation:**Filmpreparation

involvedtheapplicationofasolventcastingmet.Thepolymerspentthe night submerged in the fourth volume of solvent.To achieve a uniform dispersion,thepolymersolutionwasmixedforaround30minutesusing a magnetic stirrer. Following the addition of each component, the plasticizer, film modification, and sweetening agent were added and mixed for ten minutes.Amagnetic stirrer was used to mix the polymer solution for 60 minutes. To get rid of any air bubbles, the polymer solution was sonicated for thirty minutes. Next, polymer solution was addedtoacircularglass petriplatewitha9.0cm diameterthathadbeen previouslylubricated.Weusedglycerintolubricatethepetriplates.After being allowed to dry at room temperature, the films were cut into 2 cm by2cmpieces,peeled,andwrappedinbutterpaperbeforebeingkeptin the desiccator. The critical quality attributes considered for the formulation was, clarity of the film, peelability, stiffness and disintegration time.

- **Step 2 Selection of Vehicle:** Since the medication modafinil was very soluble in water, water was used as the solvent while making the films. However, using water extended the film's drying period. Ethanol was thus employed as a cosolvent to shorten the film's drying time.
- **Step 3 Selection of Film Forming Polymer:** A range of film-forming polymers, including carageenan, xanthan gum, polyvinyl alcohol, and HPMC, were evaluated for their capacity to form films. The best film- forming agent among the several polymer grades examined was determined to be HPMC. Mouth dissolving films were prepared using the solvent casting procedure. The results showed that HPMC E3, E5, andE15producedgood,clear,non-stickfilm.At5%concentration, HPMC E3 (F9) and E5 (F14) produced nice films, but they were ultimately determined to be soft. The finest film-forming polymer is HPMC E15, which produced transparent, easily peeled films at lower concentrations without sacrificing much softness.
- **Step4SelectionofPlasticizer:**PEG400wastestedbecausestickyfilms (F1,F2)weregeneratedwhenHPMCandglycerinwerecombined.PEG 400resultedin somewhatsofter,non-stickyfilms thatwereeasyto peel (F3, F4).
- **Step 5 Selection of Film Modifier:** Using maltodextrin with HPMC grades resulted in transparent films. When combined with the HPMC grades, honey created translucent films that were the right amount of stiff, allowing them to peel off without ripping and having no effect on the disintegration time (F15–F20).
- **FeasibilityTrial1withHPMCE15[9]**

Table 3 lists the trials' composition using HPMC E15. The results showed that HPMCE15isagreatfilm-formingpolymerthatproducesfilmsthatareclear,rigid, and simple to peel. It was discovered that 3% was the minimum concentration needed to create films. Films with 10% glycerin as plasticizer produced sticky films, whilst films containing 10% PEG400 produced fewer sticky films. It was therefore determined to employ PEG 400, but at a lower concentration.

CODE	F1	F2	F3	F4
HPMCE15	3%(300mg)	4%(400mg	3%(300mg)	4%(400mg)
Glycerin	10%(1ml)	10%(1ml)	-	-
PEG400	-	-	10%(1ml)	10%(1ml)
Water qs	10ml	10ml	10ml	10ml
Film properties	Stiff	Stiff	Stiff	Stiff
Peelability	Y	Y	Y	Y

Tachyness	VSticky	Vsticky	Non sticky	Non sticky
Transparency	Y	Y	Y	Y

X:NoresultY:Yesispositive

Table3Composition of Placebo Film with HPMCE15

- **FeasibilityTrial2withHPMCE3[10]**

Table 4 lists the trials' composition using HPMC E3. When combined with PEG 400 at 10% concentration, HPMC E3 was found to produce excellent translucent and easily peelable films at 5% concentration (F9). Compared to films made with HPMC E15, those made with HPMC E3 were less durable.

CODE	F5	F6	F7	F8	F9
HPMCE3	1% (100mg)	2% (200mg)	3% (300mg)	4% (400mg)	5% (500mg)
PEG400	10%(1ml)	10%(1ml)	10%(1ml)	10%(1ml)	10%(1ml)
Ethanol	5ml	5ml	5ml	5ml	5ml
Water qs	10ml	10ml	10ml	10ml	10ml
Film properties	X	X	Thin	Thin	Stiff
Peelability	No Film	No Film	Difficultto peel	Difficultto peel	Easily peeled
Tachyness	-	-	-	Non sticky	Non-Sticky
Transparency	-	-	-	Y	Y

X:NoresultY:Yesispositive

Table4CompositionofPlaceboFilmwithHPMCE3

- **FeasibilityTrial3withHPMCE5[11]**

Table 5 lists the trials' composition using HPMC E5. HPMC E5 generated stiff, clear, and peelableplacebo films at concentrations of3%(F12) and 4%(F13),but at a high concentration of 5% (F14), the films were difficult to peel.

CODE	F10	F11	F12	F13	F14
HPMCE5	1% (100mg)	2% (200mg)	3% (300mg)	4% (400mg)	5% (500mg)
PEG400	10%(1ml)	10%(1ml)	10%(1ml)	10%(1ml)	10%(1ml)
Ethanol	5ml	5ml	5ml	5ml	5ml
Water qs	10ml	10ml	10ml	10ml	10ml
Film properties	X	X	VeryThin	Thin	Stiff& Good

Peelability	No Film	No Film	Difficult to peel	Difficult to peel	Peelable
Tachyness	-	-	-	Non sticky	Non Sticky
Transparency	-	-	Y	Y	Y

X:NoresultY:Yesispositive

Table5CompositionofPlaceboFilmwithHPMCE5

- **Trial4OptimizationwithSelectedExcipients[12]**

The results of feasibility trials1,2, and 3 indicated that HPMCE15, when combined with plasticizer PEG400, was the most effective film-formingpolymer. Since PEG 400 created exceptionally flexible films, its concentration was lowered and honey was added as a film-modifying agent to change the film's characteristics. Researchers discovered that adding honey to the films stiffened them up enough to peel off readily without ripping (F15F20). Table 7 lists the ingredients used in experiment 4 placebo films using HPMC E15 and honey.

CODE	F15	F16	F17	F18	F19	F20
HPMCE15	3% (300mg)	3.5% (350mg)	4% (400mg)	3% (300mg)	3.5% (350mg)	4% (400mg)
PEG400	1% (0.1ml)	1% (0.1ml)	1% (0.1ml)	1% (0.1ml)	1% (0.1ml)	1% (0.1ml)
Honey	2% (0.2ml)	2% (0.2ml)	2% (0.2ml)	4% (0.4ml)	4% (0.4ml)	4% (0.4ml)
Ethanol	5ml	5ml	5ml	5ml	5ml	5ml
Water qs	10ml	10ml	10ml	10ml	10ml	10ml
Film properties	Good. Stiff	Good. Stiff	Good Stiff film	Good Stiff film	Good. Stiff	Good. Stiff
Peelability	Y	Y	Y	Y	Y	Y
Tachyness	Non Sticky	Non Sticky	Non Sticky	Non Sticky	Non Sticky	Non Sticky
Transparency	Y	Y	Y	Y	Y	Y
Disintegration time	1min 10 sec	1min 45 sec	2min	1min	1min20 sec	2 min

X:No resultY:Yesispositive

Table6 CompositionofPlaceboFilmwithHPMCE15andHoney

2.2.3. Formulation Development of Modafinil Mouth Dissolving Film: The formulation shown in Table No. 7 was chosen to prepare the modafinil mouth dissolving film based on the F1–F20 placebo trials.

S.No	Ingredients	Quantity	Use
1	RamosetronHCL	0.1mg /film	AntiEmeticDrug
2	HPMCE15	3.5 -4%	FilmformingAgent
3	Honey	2-4%	FilmModifying agent
4	PEG400	2%	Plasticiser
5	PropyleneGlycol	1%	Cosolvent
6	MethylParaben	0.01%	Preservative
7	Ascorbic Acid	10mg	Antioxidant
8	CitricAcid	10mg	SalivaStimulatingAgent
9	Aspartame	5mg	Sweetener
10	Ethanol	5ml	Cosolvent
11	Water qs	10ml	Solvent

Table7FormulationofModafinilMouthDissolvingFilm

Optimization of Modafinil Mouth Dissolving Film using 3^2Factorial Design: Modafinil's mouth dissolving film was optimised by experiment design. There were nine formulations in a full factorial experimental design, with two variables used at three different levels. The two numerical elements that were employed as independentvariables were the concentration of honey (X2) and the concentration of HPMC E15 (X1). The responses Y1 (disintegrationtime in seconds), Y2(tensile strength of film sing/cm2),and Y3(drugreleasein%at9min) were chosen for statistical optimisation.Tables8and9 present the experimental design layout and composition of the Modafinil mouth dissolving films, respectively [13].

Ingredients	R1	R2	R3	R4	R5	R6	R7	R8	R9
Ramosetron HCL(mg)	1.58	1.58	1.58	1.58	1.58	1.58	1.58	1.58	1.58
HPMCE15 (%)	3.5	3.75	4.0	3.5	3.75	4	3.5	3.75	4
Honey(%)	2	2	2	3	3	3	4	4	4
PEG400(%)	1	1	1	1	1	1	1	1	1

Methyl Paraben(%)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citricacid (%)	1	1	1	1	1	1	1	1	1
Ascorbicacid (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol (%)	1	1	1	1	1	1	1	1	1
Ethanol(ml)	5	5	5	5	5	5	5	5	5
Water qs (ml)	10	10	10	10	10	10	10	10	10

Table8 Compositionof32FactorialModafinilMDFFormulation

	IndependentVariables					
Factors	CValues			ActualValuesin%		
X1	-1	0	+1	3.5	3.75	4.0
X2	-1	0	+1	2	3	4
DependentVariables(Response)						
Y1		Y2		Y3		
DisintegrationTimein Seconds		Tensilestrengthoffilmin g/cm^2		DrugReleaseinPercentageat 9 minutes		

Table9 LayoutofTwoFactorThreeLevelDesign

2.2.3. CharacterizationofModafinilMouthDissolvingFilm[14].

The produced films underwent assessments for stability, drug release, folding endurance,disintegrationtime,weight,thickness,surfacepH,tensilestrength,and microscopy.

- **Physical Appearance:** We visually examined the oral dissolving films to ensure they were consistent, clear, and tacky.
- **Weight and thickness:** The prepared films were sliced into 2 cm by 2 cm pieces, and a Sartorius electronic scale was used to weigh them. We weighed each of the three films separately, noting the average weight and standard deviation. Using a micrometre, the thickness of the film was measured three times. The standard deviation and average of the three measurements for each film were noted.
- **Surface pH:**After placing the film in a glass petriplate, it was wet with 0.5 ml of phosphatebufferandleftfor30seconds.ThepHwasthenmeasuredbytouchingthe surfacewiththepHmeter'selectrode.Threereadingsfromthreedifferentfilmswere averaged, and the

standard deviation was noted (1, 91).

- **FoldingEndurance:** The test involved carefully folding each individual film in the same plane until a crackbecameevident.Thefoldingenduranceofthefilmisdefinedasthenumber of folds required to cause a visible break (103,104). ensile Power

2.2.3.1. Tensilestrengthisthemaximumstressappliedonthefilmtillitbreaksandiscalculated using the formula given below:

$$\text{Tensilestrength} = \frac{\text{LoadatfractureX}}{\text{FilmthicknessXfilmwidth}} \quad 100$$

An average and standard deviation of three reading was recorded using Tensile strength tester Lami Coat equipment's Mumbai India.

2.2.3.2. Disintegration test: Using phosphate buffer pH 6.8 as the medium and a temperature of 37±2°C, the disintegration test was conducted using the disintegration test apparatus IP[15].

2.2.3.3. In vitro Drug Release: Using a modified version of Dinge et al.'s dissolving equipment, the in vitro drug release of modafinil mouth dissolving films was ascertained (Fig 4.2). Phosphate buffer with a pH of 6.8 was the dissolving media employed.Thefilmsweresuspendedinadissolvingflaskandputina50mlbeaker with20mlofphosphatebuffer (pH6.8)init.Usingthedissolvingapparatus II,the stirrer was operated at 50 rpm without a basket attachment. Samples were taken at intervals of 3, 6, 9, 12, 15, 18, and 21 minutes. Using UV 1800, the content was determined spectrophotometrically at λmax 248 nm [16].

2.2.3.4. Assay: After dissolving the modafinil film in 10 millilitres of pH 6.8 phosphate buffer,theamountofdrugpresentwasquantifiedspectrophotometricallyusingUV 1800 at λmax 248 nm.

2.2.3.5. StatisticalOptimisation: StatEaseInc.'sDesignExpert11.0softwaretrialversion wasutilisedforstatisticaloptimisation.Theimpactoftheindependentvariables,X1- HPMC E15 concentration and X2-Honey concentration, on the responses, or dependentvariable,Y1-filmdisintegrationtimeinsecondsResearcherslookedatthe film'sY2-tensilestrengthing/cm2andY3drugreleaseat9minutes.Withtheuseof responsesurfacegraphsandtwo-wayANOVAatasignificancethresholdofP<0.05, the impact of each independent variable on the responses was calculated.

2.2.3.6. Microscopy: UsingaJFC1600scanningelectronmicroscopemanufacturedbyJeol Ltd. in Tokyo, Japan, a 2 cm by 2 cm film was examined for morphology and topography of the optimised film that had been created.

2.2.3.7. ResidualSolventAnalysis: Afterdryingthefilmsatroomtemperature,thequantity of residual solvent ethanol still trapped in the film was measured using HeaMFace Gas Chromatography for the optimised film formulation.

2.2.3.7.1. PreparationofCalibrationStandardStockSolution: Weighprecisely100 mgofethanolintoa100mlvolumetricflask,addwatertofillthecontainer, and thoroughly mix to get a 1 mg/ml solution concentration. Next, pour 10 millilitres of this solution into a 100-millilitre volumetric flask, top up the capacity with water, and thoroughly mix to achieve 0.1 milligrammes per millilitre. Preparing dilutions for the calibration curve included using this stock solution.

2.2.3.7.2. Calibrationcurvepreparationforsolventethanol: Differentdilutions,1, 3, and 6 µg/ml in water, were prepared using the stock solution mentioned above. Fill a different heaMFace container with 5 ml of each dilution. The butylseptaofpolytetrafluoroethylene(PTFE)weresealedandcappedwith an aluminium crimp cap.

2.2.3.7.3. Samplesolutionpreparation: WeighfiveModafinilmouthdissolvingfilms precisely, then dissolve them in water in a 50 mL volumetric flask. After giving it a good shake for five minutes to dissolve the mouth-dissolving films, fill the space with water and thoroughly stir. Pour 5 millilitres of this sample solution into the vial for heaMFace. The aluminium crimp cap was used

to shut and seal the PTFE butyl septa.

MethodofAnalysis

2.2.4. PreparationofReagentsandSolutions[17]

2.2.4.1. Simulatedsalivaryfluid:Eightgrammesofsodiumchloride,0.19grammesofpotassium phosphate monohydrate, and 2.38 grammes of sodium phosphate dibasic were precisely weighed,dissolvedinasmallamountofpurewater,andthendilutedupto1000millilitres with purified water to create the simulated salivary fluid, which had a pH of 6.8.

2.2.4.2. DevelopmentofSpectrophotometricMethodforEstimationofFixedDoseCombination of Modafinil (MF)

2.2.4.3. Thesimultaneousequationapproachisusedtoestimatethefixeddosagecombinationof pyridoxine hydrochloride and doxylamine succinate.

2.2.4.4. A1 Stock Solution Preparation Pyridoxine hydrochloride with Doxylamine Succinate Transfer100mgofdoxylaminesuccinate(DS)toa100mlvolumetricflaskafterprecisely weighing it.After that, dissolve in pH 6.8 artificial salivary fluid and add 100 ml to get a concentrationof1mg/ml.Onceina100mlvolumetricflask,transfer10mlofthissolution, which is equivalent to 10 mg, and dilute it to 100 ml to get a stock solution of 0.1 mg/ml, or 100 µg/ml. This stock solution served as the basis for the dilutions needed for the simultaneous equation approach. Pyridoxine hydrochloride (PH) also required the preparation of a stock solution at a concentration of 100 µg/ml.

2.2.4.5. A2 Pyridoxine Hydrochloride and Doxylamine Succinate Simultaneous Estimation Method Using the stock solution, 10 ppm of each medication was prepared and scanned usingaUVspectrophotometer.Basedontheabsorbancemaximaofbothmedications,the wavelengthforestimatewaschosenusingtheoverlayspectraofthepharmaceuticals.After preparing a series of standard solution dilutions from 5, 10, 15, 20, 25, 30, 35, and 40 µg/ml, absorbance was measured at both chosen wavelengths. The stock solution of doxylamine succinate was used. In the same way, a series of standard solution dilutions were made starting at 5, 10, 15, 20, 25, 30, 35, 40, and 50 µg/ml using the medication pyridoxine hydrochloride reserve solution.At the chosen wavelength, the absorbances of the produced dilutions were measured. The absorptivity coefficient was used to create a simultaneous equation for medication estimation.

Cx=(A2ay1-A1ay2)/(ax2ay1-ax1ay2) ---------- [2.1]

Cy=(A1ax2-A2ax1)/(ax2ay1-ax1ay2) ---------- [2.2]

Where Cx= concentration of DSA1=absorbance of samples at 260.6 nmax1 = absorptivity of DS at 260.6nm and ax2 = absorptivity of DS at 324nmCy = concentration of PHA2= absorbance of samples at 324.0 nmay1= absorptivity of PH at 260.6nm and ay2 = absorptivity of PH at 324nm.

2.2.5. Drug and Excipient Compatibility Study[18]: To ensure that the medicine does not react with the formulation excipients under experimental conditions, which might shorten theproduct's shelflifeorhaveotherundesirableeffects on theformulation, it is crucial to establish that the drug and excipients are compatible. Fourier transforminfraredspectroscopy(FTIR)anddifferentialscanningcalorimetry(DSC) are used to investigate the formulation's compatibility.

- Formulation of Doxylamine succinate with Pyridoxine HCL: A Drug and Excipient Compatibility Study with DSC Using DSC, a drug excipient compatibility study was conducted for the formulation of a fixed dosage combination of pyridoxine hydrochloride and doxylamine succinate in a dry state.Ashian Labs in Mumbai used the DSC Instrument UniversalV4SATAto conduct the study. The drug by itself and the drug combined with polymer thermograms were taken in a nitrogen environment at a scanning rate of one degree Celsius per minute, throughout a temperature range of -100 to 400 degrees Celsius. We examined the recorded thermograms to look for any odd changes in peak position or appearance.
- FTIR Spectroscopy-Based Drug Excipient Compatibility Study for Modafinil Formulation. In

order to investigate the compatibility of drugs and excipients, combinations are

2.2.6. FormulationofMouthDissolvingSublingualFilmofFixedDose[19]: Combination of Modafinil (MF)

2.2.7. Preliminary Screening forPlacebo Films i.e. without drug: The procedure used for preparation of placebo films of MF was same as that used for placebo films of Modafinil MDF.

Steps1SelectionofExcipients: BecauseMFareusedtotreatnauseaandvomiting inpregnantwomen,greatcaremustbetakentochooseanexcipientthatwon'tharm thedevelopingfoetus.SincebothofthemedicationsMFarehighlysolubleinwater, distilled water was employed in the preparation process for solvent casting. Since the formulation was meant to relieve pregnant women's nausea and vomiting, no ethanol or other organic solvent was used—organic solvents can be harmful to the developing foetus. The MDF were lowered in temperature to 40°C by drying them in an oven. Since the medications MF had an unpleasant taste, sugar was added to flavouring agents to conceal the taste.formulation Creation of MF: Dissolving SublingualFilmforMouthUseInconjunctionwithplasticizerPEG400,HPMCE15 was utilised as a film forming agent because of its superior film forming qualities, as demonstrated by feasibility trials 1 and 4. If honey is to be used as a natural raw material, it must be preserved during processing. Honey was not added to the preparation to alter the film's properties because the majority of oral preparation preservatives are teratogenic. can alter the film's properties, giving it stiffness and resistance, for example.Among the available sweeteners, the one that doesn't have thepotentialtocausepregnancyteratogenicityandmaybeusedbydiabeticpatients was selected since some pregnant women may develop gestational diabetes. Sucralose,anartificialsweetener,wassoselected.Asauterinetonicandflavouring ingredient, raspberry syrup has no teratogenic potential. We periodically tasted the initial trial batch to determine the ideal ratio of sweetness to flavour.

CODE	F21	F22	F23	F24	F25	F26
HPMCE 15	3% (300mg)	4% (400mg)	5% (500mg)	0.5% 50mg)	1% (100mg)	2% (200mg)
HPMCE5	0.5% (50mg)	0.5% (50mg)	0.5% (50mg)	5% (500mg)	4% (400mg)	3% (300mg)
PEG400	5% (0.5ml)	5% (0.5ml)	5% (0.5ml)	5% (0.5ml)	5% (0.5ml)	5% (0.5ml)
Water qs	10ml	10ml	10ml	10ml	10ml	10ml
Film properties	Good &stiff	Good & Stiff	Good & Stiff	Good & Stiff	Good & Stiff	Good & Stiff
Peelability	Y	Y	Y	Y	Y	Y
Tachyness	Non sticky	Non sticky	Non sticky	Non sticky	Non sticky	Non sticky
Clarity	Y	Y	Y	Y	Y	Y
DT	1.55min	2min 20s	3min	2 min	2.30min	3min 40 s

X:NoresultY:Yesispositive

Table10CompositionofPlaceboFilmwithHPMCE15andHPMCE5

InContrasttoformulationsF24,F25,andF26,experiment5demonstratesthatformulations F21,F22,andF23weredeterminedtobefirmerandsimplertopeelwithouttearing.Table 11 provides the composition determined by the feasibility study 5.

Sr.No	Ingredients	Quantity
1.	Modafinil	10mg/film
2.	HPMCE15	3.5-4%
3.	HPMCE5	0.5-1%
4.	PEG400	2.5-5%
5.	CitricAcid	10mg
6.	Sucralose	10mg
7.	Raspberrysyrup	1ml
8.	Water qs	10ml

Table11FormulationofMFMDDFFilm

3. ResultsandDiscussion

3.1. ResultsandDiscussion ofModafinil MouthDissolving Film

- Method ofAnalysisof Modafinil
- SpectrophotometricEstimationofModafinilinPhosphateBufferpH6.8
- A UV spectrophotometer (UV1800) scanning the spectrum from 200–400 nm revealed that the drug solution of modafinil, at a concentration of 10µg/ml, in phosphate buffer pH 6.8, had maximum absorption at 248 nm. Therefore, the wavelengthofmaximumabsorbance,orλmax,wasdeterminedtobe248nm.A standard calibration curve was created using a concentration of 222µg/ml to estimatethemedication.Table17&Figure8showtheaverageabsorbancevalue ofthethreemeasurementstogetherwiththestandarddeviation(SD).Regression coefficient was determined to be 0.999 and slope to be 0.046.

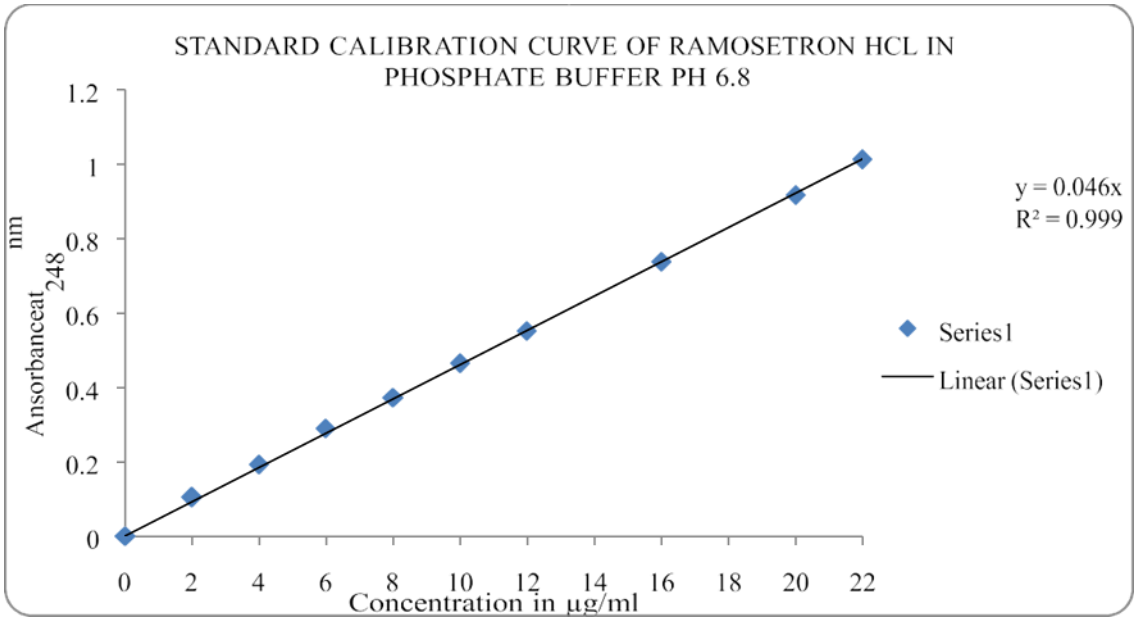

Figure2CalibrationCurveforEstimationof Modafinil

Sr.No	Concentration (µg/ml)	Absorbance			Average Absorbance ± SD
		1	2	3	
1	2	0.105	0.107	0.102	0.105 ± 0.003
2	4	0.189	0.192	0.194	0.192 ± 0.003
3	6	0.290	0.290	0.291	0.290± 0.001
4	8	0.371	0.374	0.372	0.372± 0.002
5	10	0.465	0.463	0.466	0.465± 0.003
6	12	0.55	0.552	0.551	0.551 ± 0.001
7	16	0.736	0.740	0.733	0.736 ± 0.004
8	20	0.919	0.917	0.916	0.917 ± 0.002
9	22	1.012	1.014	1.011	1.012 ± 0.002
Absorbance(y)=0.046*concentration(x)					
CorrelationCoefficient(R^2)=0.999					

Table12CalibrationCurveDataofModafinilinPhosphateBufferpH6.8

3.2. Drug-Excipient Compatibility Study of Modafinil formulation using the DSC Method The DSC study was carried out on pure drug and its combination with the proposed excipient to check the interaction of drugand the excipients. The DSC thermogram of Modafinil and Modafinilin combination of excipientsisgivenbelowin Figure 9 and Figure 10 respectively.

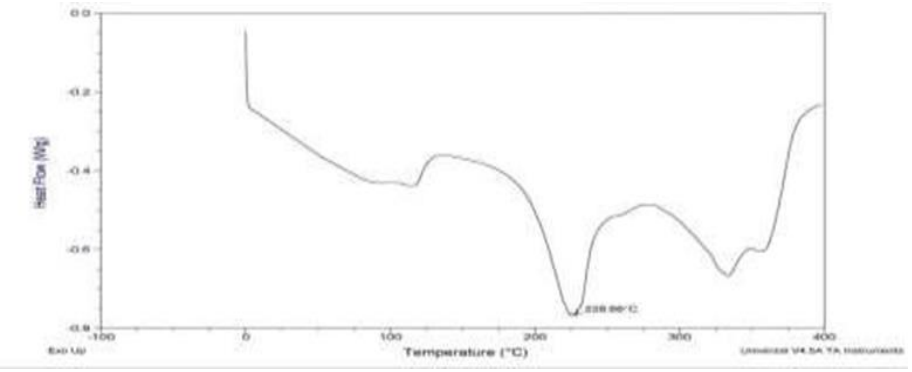

Figure3DSCThermogramofModafinilPureDrug

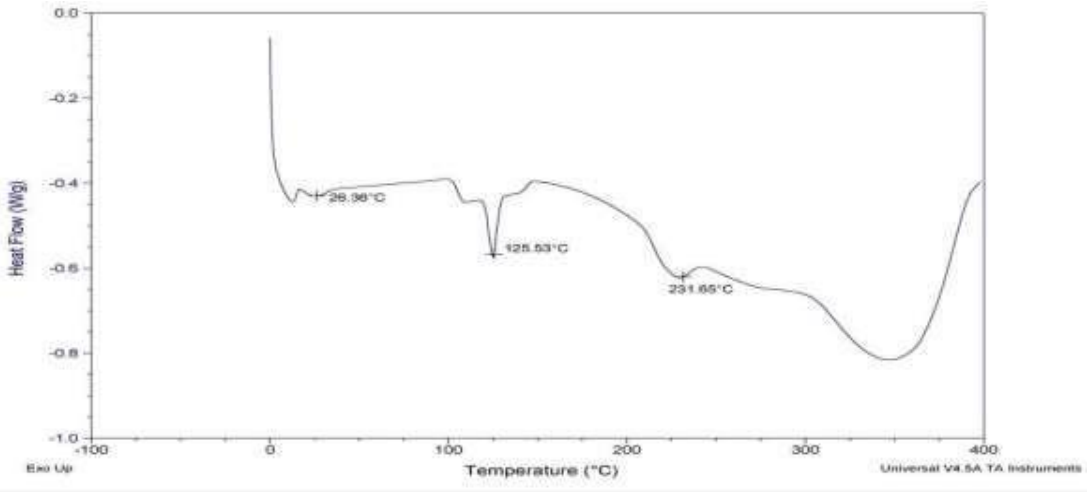

Figure4 DSCThermogramofModafinilDrugwithExcipients

ThedrugalonehadanendothermicpeakonitsDSCcurveat228.66°C,butthedrugplus excipient combination displayed an endothermic peak at 231.65°C. The inclusion of polymers may have caused a minor change in the endothermic peak. It was determined that there was no significant change in the endothermic peak, which would have indicated a drug-excipient incompatibility.

3.3. Fourier Transform Infra-Red Spectroscopy study for Drug–Excipient Compatibility ofModafinil formulation: The following are the FTIR-taken infraredspectraofthedrugmodafinilpurifiedFigure11andthedrugandexcipient combinationfigure12&Table18listsdistinctivepeaksofthedrugthat correspond to the functional groups that are present in both the drug and the combination of drug excipients. We present a comparison of the spectra of the medicine in its pure form and in combination with excipients. It is possible to establish that there is no interaction between the medication and excipient in the formulation of Modafinil mouth dissolving films since there is neither a shift nor the formation of any peak in the spectra.

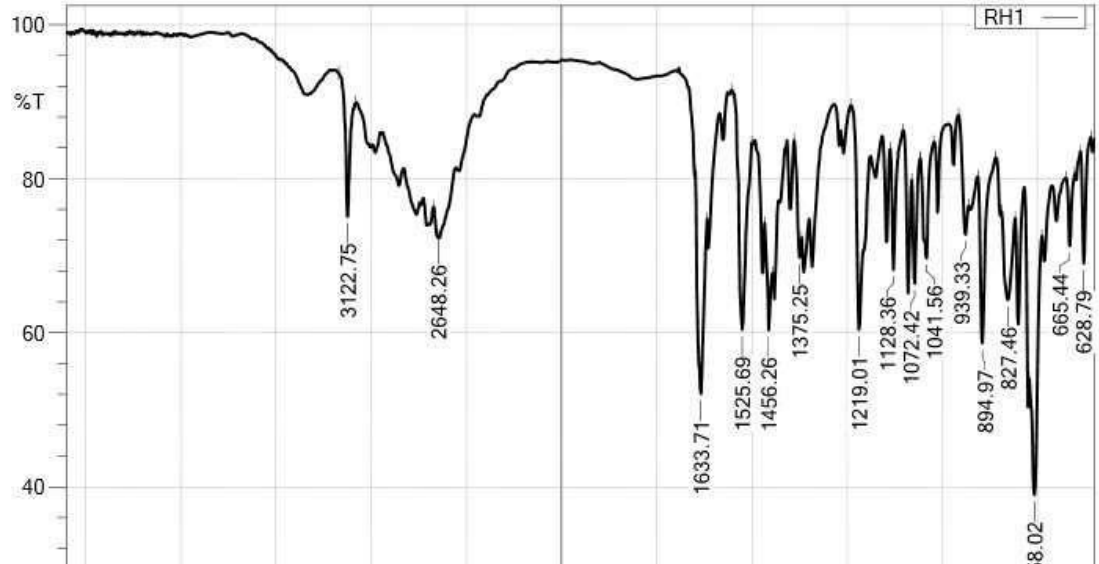

Figure5 Infra-RedSpectraofModafinil

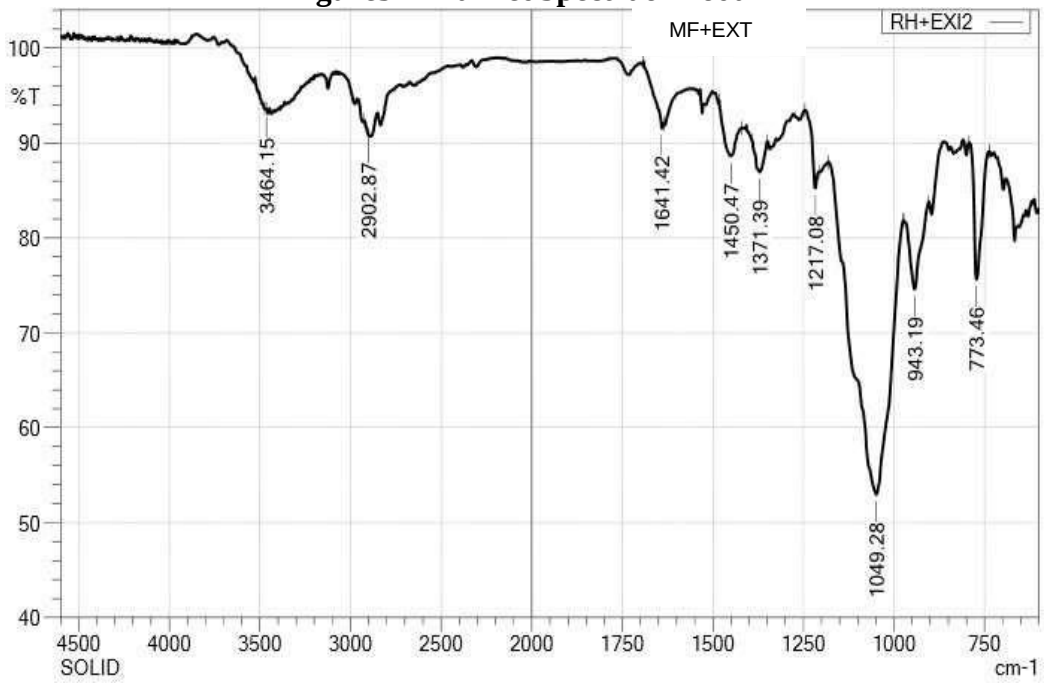

Figure6 Infra-RedSpectraofCombinationofModafinilandExcipients

Sr No	Functional Groups	Modafinil (Drug) Frequencyincm^{-1}	Modafinil+Excipients Frequency in cm^{-1}
1	N-HStretch	3311.00	3464.15
2	C-H aromatic	3122.75	3120.0
3	C-Haliphaticstretch	2648.2	2902.8
4	C=O carbonyl	1633.7	1641.4
5	C=CBenzenering	1456.2	1450
6	Cl Stretch	758.02	773.46

Table13 InterpretationofIRSpectraforDrugExcipientCompatibility

3.4. FormulationOfModafinilMDF

- Placebofilmscreenings,orthosewithoutdrugs,arepreliminary.Thepurposeof thepreliminary screening was to choose different excipients, namely the plasticizer, film modifier, and film forming agent.
- First Feasibility Trial with HPMC E15: The trial for film preparation with HPMC E15 demonstrated the product's strong film-forming capacity. Table 19 contains a tabulation of the

experimental batches' outcomes. Each film possessed excellent stiffness, transparency, smoothness, non-stickiness, and peelability.

CODE	F1	F2	F3	F4
Folding endurance	355±3.51	385±3.67	389±2.5	401±2.01
Surface pH	6.60 ±0.01	6.72±0.02	6.65±0.01	6.70±0.01
DT(s)	120±2.51	176±3.6	123±4.5	180±2.05
Thickness(mm)	0.11±0.01	0.12±0.005	0.11±0.01	0.12±0.01
Surfacetexture	Smooth	Smooth	Smooth	Smooth
Clarity	Clear	Clear	Clear	Clear

Resultsareexpressedasmean±SD(n=3)

Table14 EvaluationParametersforPlaceboFilmofHPMCE15

4. Conclusion

Patients ofall ages commonly experiencenarcolepsy.Narcolepsy can arisefrom a variety of causes, including illnesses or conditions treated with medication. A thorough examination of the implicated receptors has been helpful in selecting the right medication class for patient therapy. The objective of this study was to create a mouth-dispersing film of the antiemetic medication modafinilto treat emesis in can cerpatientsresulting from chemotherapy,aswell as a mouth-dispersing sublingual film of a combination of pyridoxine hydrochloride and doxylamine succinate to treat narcolepsy in pregnancy (NVP).

Solvent casting was the key to the successful development of the mouth dissolving film of modafinil, which would make the drug easier to administer to patients with dysphagia and cancer patients of all ages. Using HPMC E15 as the film forming agent, Honey as the film modifier, andPEG400astheplasticizerresultedinauniform,clear,stiff,andpeelablefilm that was easy to work with. The experiment's design proved to be a helpfultool for figuring out how excipients affected the movie's performance. Using theStat Ease Inc. trial version of Design Expert Software 11.0, the formulation batches were effectively optimised.After 9minutes, the formulation R1 had a disintegration time of57.0±2.16sandadrugreleaseof 104.39±1.05%, making it the most optimised batch. The mouth-dispersing sublingual film with a mixture of doxylamine succinate and pyridoxine hydrochloride was successfully created in the Second Formulation Study to treat NVP. It was possible to determine how formulation factors affected the effectiveness of the mouth-dissolving sublingual film by using an experiment design. Researchers discovered that the produced films were clear, easily peeled, uniform, and non-tacky.The disintegration time, tensile strength, and drug release from the films were found to be influenced by formulation factors and the concentration of HPMC E15 and HPMC E5. With a disintegration time of 72.56±2.61s, a tensile strength of 77.46±1.02g/cm2, and a drug release of 97.21±1.59%, DP1 was determined to be the optimal formulation. Pyridoxine HCL (99.09±2.81%) with Doxylamine Succinate. Oral dissolving sublingual films containing Modafinil may be a viable substitute for NVP, offering pregnant women who are already experiencing distressing symptoms quick relief.

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Conflict of interest: None

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