EVALUATION AND DEVELOPMENT OF POLYHERBAL ORAL FILM : A NOVEL APPROACH FOR THE TREATMENT OF TOOTHACHE, DENTAL CARIES AND ORAL INFECTIONS.

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Abstract- **Oral disease and oral infections is still a major Public health problem across the globe. Toothache, dental caries are one of human's oldest and most prevalent diseases.**

The present study aimed to develop and evaluate Polyherbal oral dissolving Films commonly known as orodispersible Films [ODFs] From Four Selective combinations of herbal extracts For the management of oral health issues.

This study Focused on the incorporation into orodispersible Films [ODFs] of the herbal extracts Of *Thyme Vulgaris, Annona squamosa (b), Mentha piperita and Syzygium aromaticum (Clove)* Against bacteria like Streptococcus mutans.

The Films were formulated using a blend of Polymers and plasticizers and their physical chemical, mechanical and antimicrobial Properties were evaluated. The antimicrobial Properties of the poly herbal Films and Standard Marketed Formulations Such as mouthwash were evaluated against the dental Pathogens S. mutans.

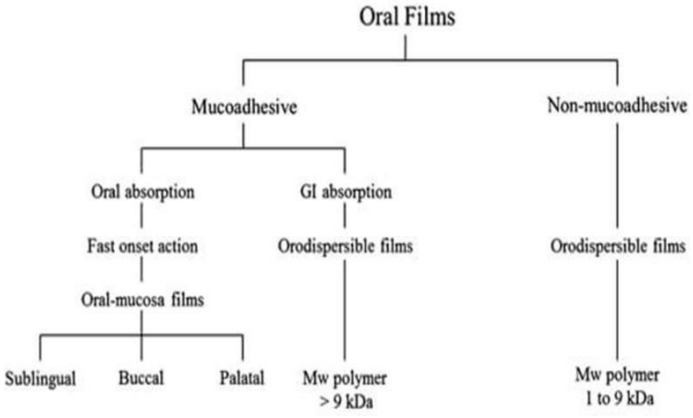
The Zone of inhibition produced by Standard marketed Formulation is less than the Polyherbal Films. These results indicated that the " mouth dissolving Poly herbal Films Could be effective in the treatment of toothache, dental caries and oral infections.

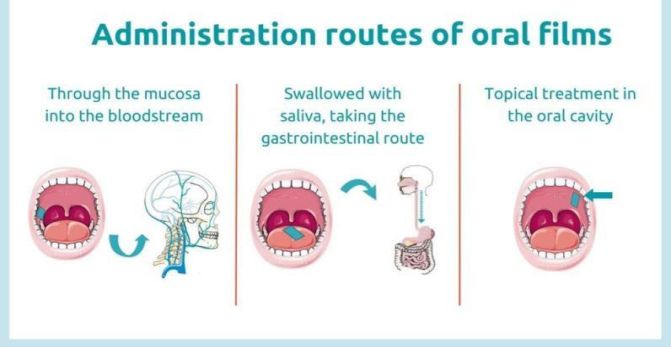
The Polyherbal oral Films demonstrated Promising result's With good tensile strength, Flexible and antimicrobial activity against Oral Pathogens. The Film also showed Sustained release of herbal extract, indicating their potential For Prolonged therapeutic effects, The developed Polyherbal Oral Films Offers a Novel and effective approach for the management of oral issues provide a convenient and patient friendly dosage form.

Index Terms- **Annona squamosa (b), Antimicrobial activity, Convenient and patient friendly dosage form, Hot Melt Extrusion Mentha piperita, Novel and effective approach, Orodispersible Films [ODFs], Oral Pathogens, Syzygium aromaticum (Clove), Solvent casting, Sustained release of herbal extract, Tensile strength, Thyme Vulgaris.**

I. I INTRODUCTION

Over the past few years, interest in leading edge technology has increased in efforts to improve effectiveness, Safety and Patient convenience. Orodispersible Films [ODFS] are a Novel advanced Pharmaceutical dosage Form. A thin Film that readily dissolves in the oral cavity is commonly known as orodispersible Film [ODFS] by the European Medicines Agency [EMA] The oral Films are essentially Complex polymeric matrices that may be used efficiently as drug release platforms. The hydrophilic Polymers are its main core, both Synthetic and Natural Polymers can be used in orodispersible dosage Forms such as
Cellulose, HPMC, HPC, Starch, Eudragit, Carbomer 974 P The common dosage Forms For oral administration are tablets, Pills, Powders, mouthwashes, gels and capsules, ODFS are interesting alternative dosage Form especially For patients who have difficulty in swallowing and for Children also. These Films get dissolved within a quick period of time in mouth without Chewing or drinking water.





Noval oral Fast-dissolving Films offers –
Simple administration method, Patient convenience, Reduce the use of Synthetic antimicrobial agents which can lead to side effects, toxicity and antimicrobial resistance, Herbal medicine offers promising alternative due to their natural origin, efficacy and low toxicity, Provide localized delivery of therapeutic agents leads to Fast pain-relief and treatment outcomes, Stages in the Pathogenesis.

II. PLANT PROFILE

1. Thymus vulgaris (Thyme)

Family: Lamiaceae
Chemical constituent: monoterpens like thymol, p-symene, carvacrol
Properties: Antimicrobial, Anti- inflammatory, antioxidant, and commonly use as flavoring agent.

2. Mentha piperita (mint)

Family: Lamiaceae
Chemical constituent: menthol, menthone, methyl acetate, eucalyptol.
Properties: analgesic, anti-inflammatory, antimicrobial, aromatic and flavoring agent.

3. Annona squamosal

Family: Annonaceae
Chemical constituent: Linalool, Eugenol, Annotemoyin, Squamocin,
Properties: Antibacterial against streptococcus mutans, lactobacillus casei which damages teeth and gums. Also show antidiabetic activity which is effective in dental caries

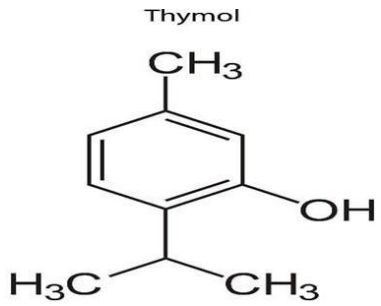
4. Clove

Scintific name: Syzygium Aromaticum / Eugenia Cariophyta
Family : Myrataceae
Chemical constituents : Eugenol [50- 87%] Eugenol Acetate [5-15%], Caryophyllene, Humulene.
Properties: Anti-bacterial , Anti- inflammatory, antioxidant, analgesic (topical dental) reduced ulcer and bad breath.

III. DRUG PROFILE

A. Thymol

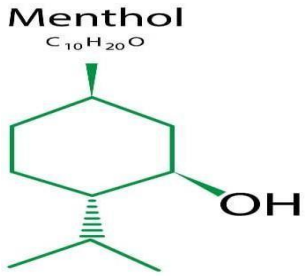
Chemical name : 2-isopropyl-s-methylphenol
Molecular formula : $C_{10}H_{14}O$
Molecular weight : 150.22 g/mol
Structure :



Pharmacological class: Anticeptic, antifungal, antibacterial, antioxidant

B. Menthol

Chemical name: (1R,2S,5R)-2-isopropyl-5-methyl cyclohexanol.
Molecular formula: $C_{10}H_{20}O$
Molecular weight : 156.26 g/mol
Structure :



Pharmacological class: analgesic, counterirritant, anti- inflammatory

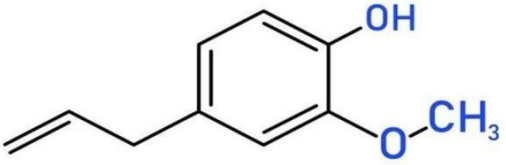
C. Linalool:

Chemical name: 3,7 – Dimethyl – 1,6 octa diene - 3 ol
Molecular formula: $C_{10}H_{18}O$
Molecular weight : 154.25 g/mol
Structure :

Pharmacological class: Anti Inflammatory, Anxiolytic, Analgesic, Antimicrobial

D. Eugenol

Chemical name: 4-allyl-2-methoxy phenol
Belongs to the class allylbenzene of organic compounds that has been isolated from syzygium aromaticum (clove)
Molecular formula: $C_{10}H_{12}O_2$
Molecular weight: 164.20 g/mol
Structure:



Pharmacological class: Antiseptic, Antioxidant, Analgesic, (Topical Dental), Anti-Inflammatory, Local Anesthetic, AntiCancer.

IV. MATERIAL AND METHOD

1. **Herbs :**
   Leaves Extract of -
   a. Thymus Vulgaris
   b. Mentha Peperita
   c. Annona Squamosa
   d. Syzygium Aromaticum (Buds)

2. **Other Excepients :**
   a. Polymers
      i. HPMC (Hydroxy Propyl Methyl Cellulose)
      ii. Eudagrit Rs 100
   b. Plastisizers
      i. PEG 400(Poly Ethylene Glycol)
      ii. Polyvinyl Alcohol
   c. Solvents
      i. Ethanol
      ii. Methanol
      iii. Hexane
      iv. Distilled Water
   d. Flavouring Agent
      i. Peppermint Oil

Methods :

A. Plant Material

Leaves of *Thymus Vulgaris*, *Annona Squamosa, Mentha Pepperita And Buds of Syzygium Aromaticum* were collected from sorroundings and dried under shade for 2 to 3 weeks and then powdered

B. Extraction Method

1. Preparation of Sample

The dried plant material kept in hot air oven below 50°C to remove moisture content.

Grind to coarse powder.

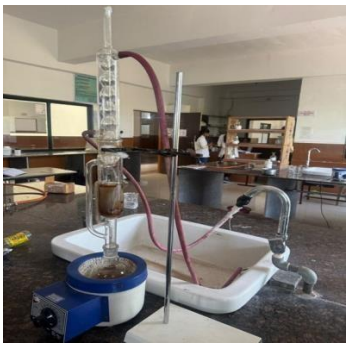
2. Weigh the material

10 – 30 gm of each dried plant powder weigh accurately and separately

3. Load the thimble

Place the powdered sample into a Soxhlet thimble [Filter paper thimble or Cellulose thimble] only one sample in one time follow the same process for next three dried powdered sample.

4. Setup the Soxhlet apparatus



Place the thimble into the main chamber of the Soxhlet extracter, fill the round bottom flask with the solvent [usually150 - 250ml] Ex. – Ethanol, Methanol, Hexane, etc. Attach the condenser and ensure water flow is properly set.

5. Start extraction

Heat the flask using a heating mantle or water bath. Allow the solvent to evaporate, condense, and Siphon repeatedly, Extraction time 6 – 8 hours or until the solvent in the siphon tube appears colourless.

6. Concentration of extract

After completion remove solvent using rotary evaporator or evaporation on a water bath.

7. Store the extract

Keep the extract in air tight vials or bottles at 4°C for further use.

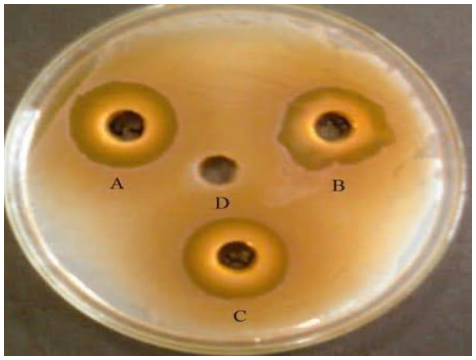
PHYTOCHEMICAL SCREENING OF EXTRACT

The extracts were subjected to Phytochemical screeining for the detection of active phytoconstituents and other primary and secondary metabolites.

All the four extracts were tested for the presence of Alkaloids, Flavonoids, Tannins, Saponins, Phenol, Terpenoids, Glycosides, Steroids, by adding different reagents and solutions to the extract.

All the four extracts were found to contain significant range of Glycosides, Alkaloids, Phenolic compounds, Flavonoids, Tannins, etc. with the bioactive compound like Menthol, Thymol, Eugenol, Linalool were found to posses significant antimicrobial, anti-inflammatory, activities.

ANTIMICROBIAL SCREENING OF EXTRACT

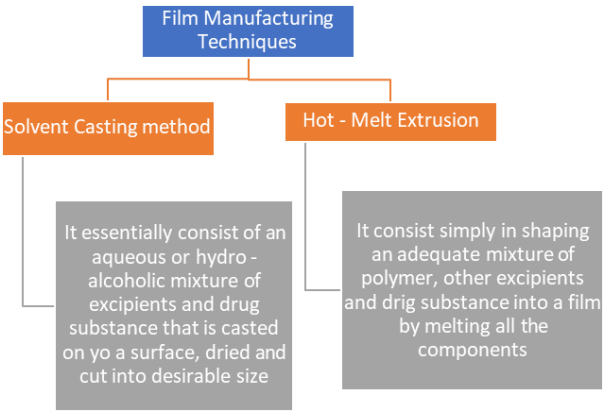


The plant extracts were mixed in the ratio 1:1:1:1 to prepare polyherbal extract and screened for its antimicrobial property by agar diffusion method.12 Mitis salivarius agar media was prepared and sterilized by autoclaving at 121°C for 20 minutes.

The sterile media was poured into sterile petri plates to a thickness of approximately 4 mm and allowed to solidify.

Bores were created in the media using a sterile borer and the plates were uniformly seeded with S. mutans suspension using sterile swab. The different concentration of polyherbal extract was then incorporated into the bores and incubated at 37°C for 24 hours. The antimicrobial screening was initially carried out for 0.5% of the polyherbal extract, followed by testing using 1, 2 and 3% mixture, lastly the zone of inhibition produced by the polyherbal extract was observed under microscope**.**

FORMULATION OF FILM

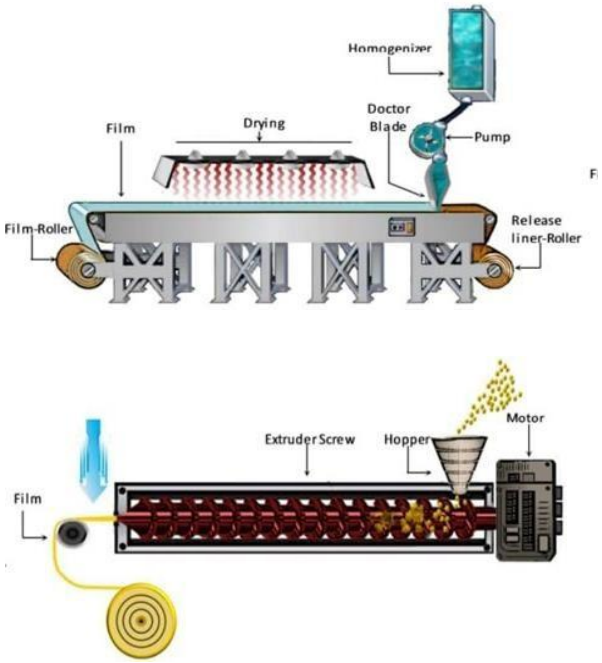


Orodespersible films are basically a polymeric matrix which may be composed by one or more polymers with different physiochemical and functional properties .

The selection of polymers for the development of oral film is a critical step and may vary depending on desired target product profile.

HPMC (Hodroxy Propyl Methyl Cellulose) is a widely applicable and suitasble polymer for formation of oral film.

The two main techniques used to prepar oral films are–



PREPARATION OF HERBAL FILMS

Oral Firms are prepared by the Solvent casting method using different Polymers.

Chemicals	**Quantity**		
API – Thymol, Eugenol, Menthol, Linalool (Extracts)	1:1:1:1	2:2:2:2	3:3:3:3
HPMC	1.3gm.	1.3gm.	1.3gm.
PEG	0.1gm.	0.1gm.	0.1gm.
Na benzoate	0.01gm.	0.01gm.	0.01gm.
Polyvineyl pyrrolidone.	0.004gm.	0.004gm.	0.004gm.
Aspartam or stevia (Sweciner)	0.02gm.	0.02gm.	0.02gm.
Glycerol	0.5gm.	0.5gm.	0.5gm.
Pepermint Oil	0.02gm.	0.02gm.	0.02gm.
Ethanol	5gm.	5gm.	5gm.
Water	q.s.	q.s.	q.s.
Total Weight	10gm.	10gm.	10gm.

Polyherbal films were prepared according to the formulation given in Table no.2.
Weighed quantity of HPMC E5 and required quantity of PEG 400 were added into a beaker with 5 g of ethanol with through mixing.
Weighed quantity of sodium benzoate, aspartame and polyvinyl pyrrolidone was dissolved in minute quantity of distilled water.
The prepared solutions were mixed homogeneously to obtain a clear solution and incorporated with polyherbal extract.
Glycerol 0.5 mL and 0.02 g peppermint oil were added, then the final weight was made up to 10 g.
Polymeric mixture (6 g) containing extracts was casted into a 7 cm diameter petri plate and dried at 50°C.

EVALUATION PARAMETER OF FILM

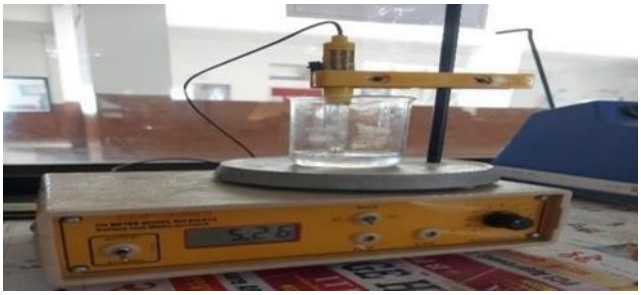
A. Organoleptic Evaluation

Sr. no.	Test	Results
1	Colour	light green to brownish/ yellow.
2	Odour	Peppery, Cinnamic
3	Taste	sweet
4	Physical Appearance	Smooth, Transparent, no air bubbles

B. Physio – Mechanical Properties

1. Surface pH

The surface pH of the oral dissolving films (ODFs) was measured using a pH meter equipped with a universal pH electrode. Three ODFs were allowed to swell in 1 mL of distilled water at 20°C for 2 hours. The electrode was then placed in contact with the ODF surface and allowed to equilibrate for 1 minute before recording the pH reading. A surface pH range of 4-8 is considered acceptable



2. Thickness

The thickness of the ODFs was measured using a micro-screw meter Twenty ODFs were evaluated, with measurements taken at five different points: four corners and the center of each film.
The average thickness was recorded 0.2 plus minus 0.3 mm

3. Weight variation

Determined by weighing the film sections of 1- 2cm size, which were prepared by cutting at five different places.

OF1	OF2	OF3
20.03 ± 0.09	0.021 ± 0.08	0.023 ± 0.08

4. Folding endurance

It Determined by repeated folding of the film at the same place until the film breaks. The number of times the film is folded without breaking was considered.

Sample no.	Number of folds before breaking
1	125
2	210
3	217

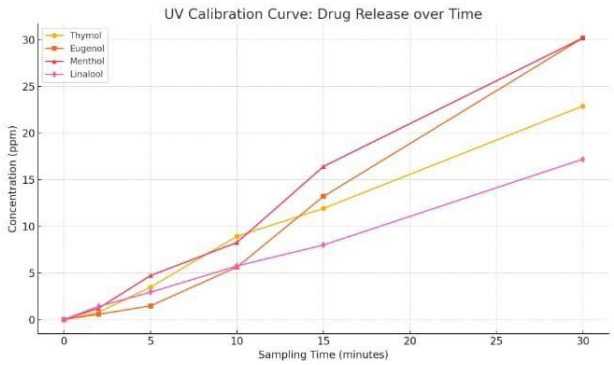
5. Dissolution Test

Dissolution test aims to determine the release profile of active Phytoconstituents from the oral films
USP dissolution Type 1(Basket) or type 2(Paddle) Apparatus with the stimulated saliva or phosphate buffer (pH= 6.8) medium was used (200-300 ml) at temperature 37 ± 0.5ºC on 50-75 RPM
Time points : 0, 2, 5, 10, 15, 30 miniutes

Sampling

Withdraw 5ml sample at each time points, filter and analyze by UV or HPLC

	Release rate of drugs			
Sampling Time	Thymo (PPm)	Eugenol (ppm)	menthol CPPm)	linalool (Ppm)
0	0	0	0	0
2	0.76	0.56	1.21	1.41
5	3.47	1.46	4.71	2.92
10	8.92	2.72	8.26	5:74
15	11.9	5.62	16.41	7.99
30	22.90	13.2	30.2	17.2



Interpretation

Faster and effective release of actives within 15 minutes
Ideal for local and fast acting dental applications

6. Disintegration Test

Use USP disintegration apparatus or petri dish method (simulated saliva pH ~6.8). Place one film in a petri dish or Disintegrating apparatus containing simulated saliva.Observe and record the time taken for complete disintegration (no visible residue).

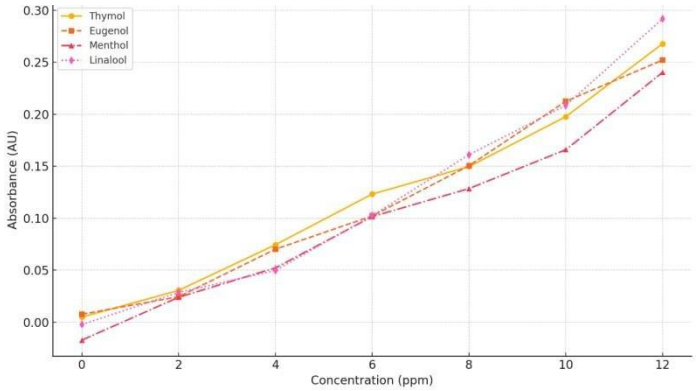
Formulation Code	Average Disintegration Time (seconds)
F1 (1% Extract)	38 ± 2 s
F2 (2% Extract)	44 ± 3 s
F3 (3% Extract)	41 ± 2 s

Validation of oral Film by UV analysis

UV analysis of the Active Phytoconsituent like Thymol, Menthol, Eugenol and linalool determined by Preparing Standard Stock Solution of thymus valgari's, Mentha Peperilta, clove (sizium--aromaticum) and Annona Squamosa, the Stock Solution was Seprately mix with 20 ml of water in a Volumetric Flask and the absorbance was measured.

UV Spectrophotometry measures the absorbance of a substance at a specific wavelength. A clalibration Curve is Plotted between known concentration and their absorbance to determine Unknown Concerntration.

Compound	ƛmax (nm)
Eugenol	280 nm
Thymol	274 nm
menthol	~ 210-220 nm
Linalool	~208-210 nm



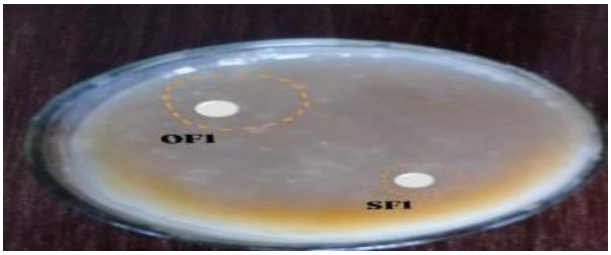
Concentration (ppm)	Thymol (ABS)	Eugenol CABS)	Menthol (Abs)	Linalool (Abs)
0	0.00	0.00	0.00	0.00
2	0.13	0.11	0.12	0.10
4	0.27	0.24	0.23	0.21
6	0.41	0.38	0.35	0.32
8	0.56	0.52	0.47	0.44
10	0.70	0.67	0.61	0.58
12	0.84	0.83	0.76	0.73

Interpretation

The UV analysis confirmed the presence of all four compounds in the polyherbal oral film formulation. The concentrations were consistent with the expected formulation content. This confirms successful incorporation and stability of herbal actives in the formulation

C. Antimicrobial Test

Antimicrobial studies of the polyherbal film against S. mutans were carried out by agar diffusion method The zone of inhibition for the standard marketed gel, mouthwash and the polyherbal films was measured.



Micro-organisms	Zone of Inhibition	
	SF1	OF1
S. Mutan	16.5 ± 0.21	13.2 ± 0.17

V. RESULT

The polyherbal oral films containing extracts of 4 selected herbal species with the polymer HPMC and Eudragit RS100 were successfully prepared by solvent casting Method the formulated Polyherbal oral films exhibited satisfactory Physicochemical Characteristics including uniform thickness (0.2-0.3mm), Good folding endurance (>200folds), Acceptable pH(6.5-7.2) and rapid disintegration time (<60 sec) indicating suitability for oral application. In – Vitro Antimicrobial activity Evaluated using the agar well diffusion method showed significant zone of inhibition against S. mutans.

VI. SUMMARY

The developed Polyherbal oral films demonstrated promising therapeutic potential for management of toothache, dental carries and oral infections.

The method was found to be simple, reproducible and accurate. The films were

found to be safe, Effective and Stable with desirable organoleptic and mechanical properties. The synergestic effect of the selected herbal extract contributed to there significant antimicrobial and analgesic activities, These findings supports the feasibility of using polyherbal oral films as a convinient and natural alternative to conventional oral care products.

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