FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF OZONATED CLOVE OIL

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1. Introduction

2. 1.1 Fast Dissolving Oral Films

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance

oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing. Fast dissolving drug delivery systems were first invented in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane.[1] It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine.[2] Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration.[3] The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called ‘membrane coating granules’ present at the uppermost 200 µm layer.[4] These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but are extremely sensitive to environmental moisture.[5] An ideal fast dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a pleasant taste. Therefore, they are very suitable for pediatric and geriatric patients; bedridden patients; or patients suffering from dysphagia, Parkinson’s disease, mucositis, or vomiting. This novel drug delivery system can also be

beneficial for meeting current needs of the industry. Rapidly dissolving films(RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for therapeutic benefits. The first of the kind of oral strips(OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films (OTF) which contained 7 benzocaine and were used for the treatment of sore throat. Formulation of fast dissolving buccal film involves material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and superdisintegrants. All the excipients used in the formulation of fast dissolving film should be approved for use in oral pharmaceutical dosage forms as per regulatory perspectives.

Advantage of fast dissolving films :

1.Convenient dosing.

2.No water needed.

3.No risk of chocking.

4.Taste masking.

5.Enhanced stability.

6.Improved patient compliance.

7.The drug enters the systemic circulation with reduced hepatic first pass effect. Site specific and local action.

8.Availability of large surface area that leads to rapid disintegration and dissolution

within oral cavity.

9.Dose accuracy in comparison to syrup.

➢ There are three subtypes of oral fast dissolving films:

1.Flash release.

2.Mucoadhesive melt-away wafer.

3.Mucoadhesive sustained release wafers.

➢ Approaches to Prepare Films

- **Solvent casting method**
- **Hot-melt extrusion**
- **Semisolid casting**
- **Solid dispersion extrusion**

• Pre-requisite for development of Oral Films:

➢ **Micronized API can improve the texture of the film and also dissolution and uniformity of the oral fast dissolving film.**

➢ **Drugs with bitter taste and foul odour are difficult to prepare in FDOF. Taste of bitter drug need to be masked for that cyclodextrins or resins can be used; they prevent the direct contact of API with the saliva.**

- **The dug should have high solubility and high permeability (BCS class I).**
- **The drug should have low dose. Drugs with high dose may increase the bulk of formulation making it unacceptable for administration.**
- **Drug should be stable at pH of saliva.**
- **Drugs should be absorbable from oral cavity.**

1.	Drug	1-30%
2.	Film forming polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva Stimulating agent	2-6%
5.	Sweeting agent	3-6%
6.	Flavouring agent	q.s
7.	Surfactant	q.s
8.	Colors,Filler	q.s

FILM FORMING POLYMER:

- **Polymers play an important role in the film formation.**

• Hydrophilic polymers are used in the preparation.

- **Now a day's both natural and synthetic polymers are used in the oral cavity.**

• Natural polymers are safe, effective and devoid of side effect so more preferred than synthetic polymers.

❑ ideal properties-

- **It should be inexpensive and readily available.**
- **It should have good wetting and spreadibility property.**

Natural polymer	Synthetic polymer
Pullulan	Hydroxypropymethyl cellulose(H
Starch	Polyvinyl pyrrolidone(PVP)
Pectin	Kollicoat
Sodium alginate	Hydroxyprpyl cellulose
Maltodextrin	Carbon methyl c ellouse(CMC)
Lycoat NG73	Poly ethylene oxide

➢ Plasticizers:

- **Plasticizers are the important excipient of the oral film.**
- **The selection of film forming polymers, is one of the most important and critical parameter for the successful development of film formulation.**
- **It improves the flexibility and a mechanical property of the film like tensile strength and elongation and reduces the brittleness of the strip.**
- **Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer.**
- **A plasticizer should be selected so that it must be compatible with the drug.**

Plasticizer can improve the flow and enhances the strength of polymer.

SALIVA STIMULATING AGENT

- **These are used to increase the secretion of saliva so that the oral film disintegrate and dissolve faster in the oral cavity.**
- **The acids which are used in the preparation of food are generally used as saliva stimulators.Citric acid, malic acid, lactic acid, ascorbic acid, tartaric acid are the saliva stimulating agent.**

➢ SWEETENING AGENTSSSWEETENING AGENT

- **Sweeteners are used for the taste masking of bitter drugs so that drugs are palatable.**
- **Natural as well as artificial sweeteners are used in the preparation of oral film.**

- **Natural sweeteners used are xylose, ribose, glucose, sucrose, maltose, steviosides, dextrose, fructose, liq. Glucose.**
- **Fructose is sweeter than sorbitol and mannitol and thus widely used as a sweetner.**
- **Artificial sweetners used in oral films are sodium or calcium saccharine salts.**

Sucralose have more than 200-600 times sweet.

- **Neotame & Altitame have more than 2000- 8000 times sweetening power as compared to sucrose.**

➢ EVALUATION OF FILM:

1)Mechanical Properties:

a)Thickness

b)Dryness/tack test

c)Tensil strength

d)Percent elongation

e)Youngs modulus

f) Folding endurance

2) Organoleptic test

3) Swelling test

4) Surface PH test

5) Contact angle

6) Transparency

7) Assay/Content uniformity

8) Disintergration test

9) In-vitro dissolution test

➢ Thickness:

The thickness of film is measured by micrometre screw gauge or calibrated digital Vernier Calipers. The thickness of film should be in range 5-200 µm.[21] The thickness should be evaluated at five different locations (four corners and one at centre) and it is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film.

➢ Dryness/tack test:

In all there have been eight stages identified for film drying and these are set-to-touch, dust-free, tack-free (surface dry), dry-to touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat, and dry print-free. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with strip. Instruments are also available for this study.

➢ Tensile strength:

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area

of strip as given in the equation below: Tensile strength = Load at failure × 100/Strip thickness × Strip width

➢ Percent elongation:

When stress is applied on a film (2 × 2 cm2) sample it gets stretched, this is referred to strain. Strain is basically the deformation of strip before it gets broken due to stress. It is measured by using hounsfield universal testing machine.[23] Generally elongation of strip increases as the plasticizer content increases. It is calculated by the formula: % Elongation = Increase in length of strip × 100/Initial length of strip.

➢ Young's modulus:

Taste is also an important factor which has to be evaluated. To evaluate the taste, special human taste panels are used. Experiments using electronic tongue measurements have also been reported to distinguish between sweetness levels in taste masking formulation.[33] Electronic tongue technique works on the principle of potentiometric titration method. In this liquid samples can be analyzed directly, whereas solid samples need to be dissolved in a suitable solvent before analyzing. In this method, reference electrode and sensors are dipped in a beaker containing a test solution for 120 s and a potentiometric difference between each sensor and a reference electrode is measured and recorded by the E-tongue software.

➢ Folding endurance:

Folding endurance gives the brittleness of a film. The method followed to determine endurance value is that the film specimen (2 × 2 cm2) are repeatedly folded at the same place until it breaks or a visible crack is observed. The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value.

➢ Organoleptic test :

The desired organoleptic properties a fast dissolving formulation should have are color, flavor, and taste. As the formulation will disintegrate in the oral cavity so it should provide acceptable organoleptic palatable characteristics. Color makes a formulation acceptable among the patients and moreover oral films should have attractive color as they are administered to children. Hence, color of formulation should be uniform and attractive. Color can be evaluated by visual inspection. The other organoleptic property is the odor. The flavor used in the formulation should provide good odor to the formulation.

➢ Tear resistance:

Tear resistance is the resistance which a film offers when some load or force is applied on the film specimen. The load mainly applied is of very low rate 51 mm/min. The unit of tear resistance is Newton or pounds-force. In other words it is the maximum force required to tear the specimen.

➢ In vitro disintegration:

Test Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should

be in range of 5-30 s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time.[27] In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates

Clove:

Clove, (Syzygium aromaticum), tropical evergreen tree of the family Myrtaceae and its small reddish brown flower buds used as a spice. Cloves were important in the earliest spice trade and are believed to be indigenous to the Moluccas, or Spice Islands, of IndonesiaClove decrease oral inflammation and bacteria. The researchers also found that the mouth rinse that contained clove decreased the number of harmful bacteria more than the commercial mouth rinse.It is important that oral hygiene be carried out on a regular basis to enable prevention of dental disease and bad breath.This is used for formulation of oral care products. Clove has strong , anti-inflammatory,antibacterial and analgesic properties.Clove attacks cavity causing bacteria, thus preventing tooth decay and cavities and a results in preventing all sort of dental problems.

Chemical Constituents of Clove oil:

- **Eugenol(about 70 to 90%)**
- **Eugenol acetate**
- **Methylamylketone**
- **Caryophyllenes**
- **Ester and alcohols**

- **Volatile oi(16 to 21%)**
- **Tannins (gallotannic acid)**
- **Resin, chrome and Eugenin)**

Ozonation

- **Ozonation of oil is done by infusing high concentration of ozone in pure oil. Ozone or trioxygen is an unstable gas with the chemical formula O3, comprising of three oxygen atoms. The gas will readily degrade back to oxygen, and during this transition a free oxygen atom, or free radical is formed. Ozone is a colourless gas and a powerful oxidant that has an odor similar to the smell of the air. It has many industrial and consumer applications related to oxidation. Ozone include high thermodynamic oxidation potential, less sensitivity to organic material and better tolerance for pH variations while retaining the ability to kill bacteria. Recent studies showed that ozonation of oils increase their therapeutic potential. In present research study it is decided to prepare ozonated clove oil and evaluate it for pharmacological activities.**

Aim and Objective:

- **Aim : Formulation and evaluation of fast dissolving oral films of ozonated clove oil.**

- **Objectives**

  - **To perform identification and characterization of clove oil and to prepare ozonated clove oil which can be used in preparation of dissolving oral film.**
  - **To evaluate and characterize compatibility of ozonated oil with selected excipients.**
  - **To formulate and optimize oral films of ozonated clove oil.**
  - **To perform in vivo study to evaluate anti- inflammatory activity of oral films.**
  - **To evaluate stability of optimum formulation.**

NEED FOR STUDY :

1.Mouth dissolving film will facilitate ease of administration for patients especially of geriatric age group thus improving patient compliance.

2.Mouth dissolving film formulation of clove oil will lead to faster rate of drug release to elicit therapeutic activity.

3.Literature survey revealed that Ozonation of oils increases their therapeutic potential. Ozonation is a process of bubbling ozone gas through oils . Ozonation of oil combines properties of oil with versatile healing properties of ozone.

4.Ultimately mouth dissolving film of clove oil by using ozonated process could be novel approach to improve therapeutic effect.

Plan of Work :

1. **Literature Review**
2. **Selection of excipient/ process/ evaluation parameters**
3. **Identification and characterization of clove oil**

- **Acid Value**
- **Saponification value**
- **UV spectrophotometric study**
- **FTIR analysis**
- **DSC study**

4. **Ozonation of Clove oil**
5. **Characterization of ozonated clove oil**

a. In-vitro evaluation

- **Acid Value**
- **Saponification value**
- **UV spectrophotometric study**
- **FTIR analysis**
- **DSC study**
- **Anti bacterial activity – Zone inhibition study- tested against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa**

- **Permeation study on artificial membrane**

b. In-vivo evaluation- animal study

Anti- inflammatory study

6. **Formulation Development and optimization of fast dissolving oral films**
7. **7. Evaluation of fast dissolving films**
8. **a. Mechanical Properties:**
9. **Thickness**
10. **Tensile strength**
11. **Percent elongation**
12. **Youngs modulus**
13. **Folding endurance**
14. **b. Organoleptic test**
15. **c. Swelling test**
16. **d. Surface PH test**
17. **e. Contact angle**
18. **f. Transparency**
19. **g. Assay/Content uniformity**
20. **h. Disintergration test**
21. **i. In-vitro dissolution study**

22. 8. In vivo evaluation of fast dissolving ozonated clove oil films

23. a. Taste and palatability evaluation

24. 9. Stability study

25. 10. Thesis writing

Experimental Design

Vivo study:

Carrageenan-induced rat paw edema model is a suitable test for evaluating anti-inflammatory drugs, which has frequently been used to assess the antiedematous effect of the drug. Carrageenan is a strong chemical use for the release of inflammatory. For the anti-inflammatory activity against the acute inflammation, animals were divided into five groups. Group A (carrageenan control) did not receive any oral treatment. Group B (Standard),Grope C (Standard).Group D ;a) Clove oil:0.01mil;b)Clove oil 0.05mi;c)Clove oil;0.1ml.

Species and Strain :Wistar rates

Gender; Male

Groip:A,B,C(a,b,c)

Wister rats:30

Group A; carrageenan control

Group B: Standard Diclofenac

Group C:a)Clove oil:0.01ml

b)Clove oil.05ml

c) Clove oil 0.1 ml

Antibacterial activity :

Clove (Syzygium aromaticum) The buds were used and they came from Zanzibar and Sri Lanka.

Extraction of essential oils:

About 20g of each herb soaked in distilled water was distilled in a stove still (steam distiller, locally fabricated). The volatile vapour that condensed at water temperature of 80°C was called essential oils. The clove buds were distilled . The distilled oils were labeled and placed in a fridge until ready for use.

Extraction of essential oils by boiling

About 20g of each herb were soaked in 50ml of distilled water and were subsequently boiled at 100°C for 15 minutes. The boiled extracts were allowed to cool at room temperature after which they were left at fridge temperature overnight to allow the solute particles to settle. The aqueous phases were pipetted, labeled and called aqueous extracts. They were kept in the fridge until ready for use.

Media

Diagnostic sensitivity test (DST, Oxoid, UK) agar plates were used for the determination of zones of inhibition produced by each extract on the control and test organisms.

Control organisms

The control organisms used for screening the extracts for the presence of antimicrobial activities were: *Staphylococcus aureua* (NCTC 6571), *Pseudomonas aeruginosa* (NCTC 10662) and *Escherichia coli* (NCTC 10418). These bacteria are routinely used in our laboratory as control organisms for antibiotic sensitivity testing of bacterial isolates from clinical specimens and they are usually sensitive to most antibiotics.

The control and test organisms were each plated on blood agar and incubated overnight at 37°C except *C. albicans* which was plated on Sabouraud medium and incubated for 48 hours. Suspensions of pure colonies in broth at 106 CFU/ml from growth on the plates were made using Mcfarland's turbidity standards.

BIBLIOGRAPHY:

1.Siddiqui MD, Garg G, Sharma P. A short review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and their Patents". Adv Biol Res 2011;5:291-303.

2. Galey WR, Lonsdale HK, Nacht S. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J Invest Dermatol 1976;67:713-7.

3. Malke M, Shidhaye S, KadamVJ. Formulation and evaluation of oxcarbazepine fast dissolve tablets. Indian J Pharm Sci 2007;69:211-4.

4. Mishra R, Amin A. Formulation and characterization of rapidly dissolving films of cetirizine hydrochloride using pullulan as a film forming agent. Indian J Pharm Educ Res 2011;45:71-7.

5. Mahajan A, Chabra N, Aggarwal G. Formulation and characterization of fast dissolving buccal films: A review. Sch Res Libr Der Pharm Lett 2011;3:152-65.

6. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. Int J Chem Tech Res 2010;2:576-83.

7. Chemical Market Reporter. Fuisz sign deal for drug delivery. Chem Mark Report 1998;253:17.

8. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Int J Pharm Sci Rev Res 2011;9:50-6.

9. Bhura N, Sanghivi K, Patel U, Parmar B. A review on fast dissolving film. Int J Res Bio Sci 2012;3:66-9.

10.Barnhart SD, Sloboda MS. The future of dissolvable films. Drug Deliv Technol 2007;7:34-7.