

DRUG DELIVERY -
FILMS, STRIPS &
DISKETTES

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1. FILMS/ STRIPS

1.1 INTRODUCTION

Definition:

Film:

It is a thin layer of drug incorporated polymeric materials similar in size, shape and thickness to a postage stamp.

Strip:

It is a thin long narrow piece of polymeric materials containing drug.

Introduction:

Thin film drug delivery uses a dissolving film or oral drug strip to administer drugs via absorption in the mouth (buccally or sublingually), in contrast or addition to via the small intestines (enterically). A film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made.

Thin film drug delivery has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and OTC medications. Similar in size, shape and thickness to a postage stamp, thin film strips are typically designed for oral administration, with the user placing the strip on or under the tongue or along the inside of the cheek. As the strip dissolves, the drug can enter the blood stream enterically, buccally or sublingually. Evaluating the systemic transmucosal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa.

The first commercial non-drug product to use thin films was the Listerine PocketPaks breath freshening strips. Since then, thin film products for other breath fresheners, as well as a number of cold, cough, flu and anti-snoring medications, have entered the marketplace. There are currently several projects in development that will deliver prescription drugs utilizing the thin film dosage form.

1.2 FORMULATION

A typical composition contains:

Drug 1-25%

Water soluble polymer 40-50%

Plasticizers 0-20%

Fillers, colours, flavours etc. 0-40%

Drugs:

Since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in OS. Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in the OS.

Several classes of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthmatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g.paracetamol, meloxicam, valdecoxib). OTFs have the capability to load APIs up to 50% of the unit dose mass, as demonstrated by Novartis Consumer Health's Gas-X thin film, which contains 62.5 mg of simethicone per dose.

Strip forming polymers

The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spreadability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Film obtained should be tough enough so that there won't be any damage while handling or during transportation.

Combination of microcrystalline cellulose and maltodextrin has been used to formulate Oral Strips of piroxicam made by hot melt extrusion technique.

The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxymethylcellulose cekol 30, Polyvinylpyrrolidone PVP K-90,

Pectin, Gelatin, Sodium Alginate, Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGIT RD10. Polymerized rosin is a novel film forming polymer.

Plasticizers

Plasticizer is a vital ingredient of the OS formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers.

Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients.

Surfactants

Surfactants are used as solubilising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

Flavour

Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors.

Colour

A full range of colors is available, including FD&C colors, EU Colours, Natural Colours and custom Pantone-matched colours. Pigments such as titanium dioxide are incorporated for coloring.

Some saliva stimulating agents may also be added to enhance the disintegration and to get rapid release. Some of these agents are citric acid, tartaric acid, malic acid, ascorbic acid and succinic acid.

Sweeting agent

An important aspect of thin film drug technology is its taste and color. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the flavor of the mouth dissolving formulations for the flavors changes from individual to individual.

Stabilizing and thickening agents

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Drug content uniformity is a requirement for all dosage forms, particularly those containing low dose highly potent drugs. To uniquely meet this requirement, thin film formulations contain uniform dispersions of drug throughout the whole manufacturing process. Since this criterion is essential for the quality of the thin film and final pharmaceutical dosage form, the use of Laser Scanning Confocal Microscopy (LSCM) was recommended to follow the manufacturing process.

1.3 MANUFACTURING METHODS

Following methods are used to manufacture the mouth dissolving films.

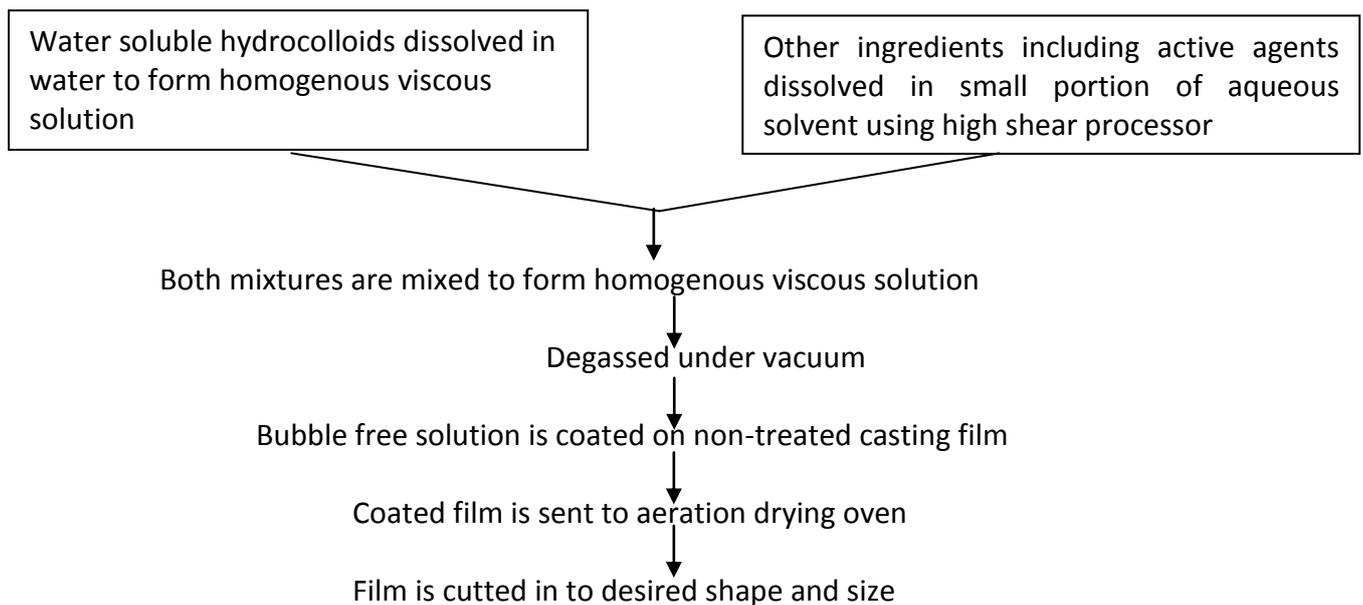
- i) Solvent casting
- ii) Semisolid casting
- iii) Hot melt extrusion
- iv) Solid dispersion extrusion
- v) Rolling

1) Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

2) Semisolid casting

In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.



3) Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion.

- Fewer operation units
- Better content uniformity
- An anhydrous process

4) Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5) Rolling Method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes. Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor.

1.4 EVALUATING PARAMETERS

1) Mechanical properties

Mechanical properties of films are evaluated Instron using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Films are held between two clamps positioned between 3cm. During measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks. Three mechanical properties namely tensile strength, elastic modulus and % elongation are calculated.

a) Tensile strength

Tensile strength is calculated by formula = force at break/ initial cross sectional area of film in mm²

b) Elastic modulus

Elastic modulus is calculated by formula

$$\text{Elastic modulus} = \frac{\text{force at corresponding strain}}{\text{Cross sectional area (mm}^2\text{)}} \times \frac{1}{\text{Corresponding strain}}$$

c) % Elongation

It is calculated as =

$$\frac{\text{Increase in length}}{\text{Original length}} \times 100$$

d) Folding endurance

Folding endurance is determined by folding the films of uniform cross sectional area and thickness until it breaks.

2) Morphology study

The morphology of the films is studied using scanning electron microscopy (SEM), at a definite magnification.

3) Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed. The degree of swelling was calculated using parameters $w_t - w_0 / w_0$, w_t is weight of film at time t , and w_0 is weight of film at time zero.

4) Contact angle

Contact angle measurements are performed at room temperature with a goniometer (AB Lorentzen and Wettre, Germany). A drop of double distilled water was placed on the surface of the dry film. Images of the water droplet were recorded within 10 seconds of deposition by means of digital camera. Digital pictures were analyzed by imageJ 1.28v software (NIH, USA) for angle determination. A minimum of five measurements, taken at different positions of the film, was carried out. The contact angle was measured on both sides of the drop and averaged.

5) In vitro disintegration time

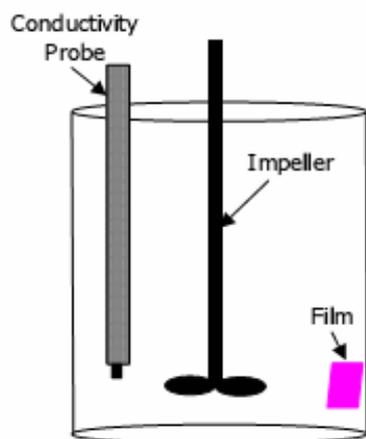
In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

6) In vitro dissolution studies

The in vitro dissolution study is carried out in simulated saliva solution pH 6.4 phosphate buffer using USP paddle apparatus at $37 \pm 0.5^\circ\text{C}$. samples are withdrawn at regular time interval interval and analyzed by UV-Visible spectrophotometer.

7) Determination of dissolution rate by conductivity method

In the past 5 years several personal care products formulated in quick release film form have entered the marketplace, of which fast-dissolve breath fresheners were first. The fast dissolve oral films completely dissolve in as little



as 1 minute. The majority of oral films on the market today contain ionizable components. This work presents a method for high resolution monitoring of the dissolution of fast dissolving oral films by measuring conductivity of the dissolution medium.

Test Procedure

- ✓ Fill a clean beaker with 300 g ($\pm 0.05\text{g}$) of the deionized water.
- ✓ Test the conductivity of the water to establish the background value.
- ✓ Adhere the film inside the dry, clean 800ml beaker so that the centre section is even with or slightly below the 100 ml line of the beaker. Arrange the Conductivity probe and the impeller in the beaker.
- ✓ As quickly as possible pour the 300 ml of the water in the beaker containing the film, impeller and the conductivity probe. When the water completely covers the film, start the timer (approx 3sec). Then restart the impeller stirring at 250rpm.
- ✓ Take a data point at every 10 sec for the first minute..

Evaluation of polymeric films for buccal drug delivery.

The objective was to evaluate the suitability of the bioadhesive polymers Carbopol 981 NF, Carbopol 1382 and sodium alginate.

The **alginate films**: greater bioadhesion and higher tensile strength and elasticity than the Carbopol films. Upon swelling the thickness increases slightly

The **Carbopol films**: Upon swelling, S.A. increases significantly being unsuitable for buccal delivery (Excessive hydration-decreasing adhesive strength-loss of adhesion-shorter duration.)

HPMC: improve the bioadhesiveness and tensile strength. For the alginate films an increase in HPMC leads to an increase in elasticity. The results indicate that sodium alginate may be a suitable carrier

1.5 CLASSIFICATION

1.5 a) FAST DISSOLVING FILMS

The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed.

OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices. OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs.

The mouth dissolving films has also a clear advantage over the Oral dissolving tablets (ODTs):

- ODTs are sometimes difficult to carry, store and handle (fragility and friability).
- Many ODTs are prepared by using the expensive lyophilisation process.

Innovative products may increase the therapeutic possibilities in the following indications.

- Pediatrics (antitussives, expectorants, antiasthmatics)
- Geriatrics (antiepileptic, expectorants)
- Gastrointestinal diseases
- Nausea (e.g. due to cytostatic therapy)
- Pain (e.g. migraine)
- CNS (e.g. antiparkinsonism therapy)

TECHNOLOGIES:

1) SOLULEAVES™

Films can be designed for fast release of drugs in mouth as well as to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

2) FOAMBURST™

Is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation.

3) XGEL™

It is non-animal derived, suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing platform. It can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate API. The systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water.

4) WAFERTAB™

The API is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The system enables multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes.

1.5 b) IMPLANTABLE FILMS

The film could eventually be used to deliver drugs for cancer, epilepsy, diabetes and other diseases. It is among the first drug-delivery coatings that can be remotely activated by applying a small electric field.

The film, which is typically about 150 nanometers (billionths of a meter) thick, can be implanted in specific parts of the body.

The films are **made from** alternating layers of two materials: a negatively charged pigment and a positively charged drug molecule, or a neutral drug wrapped in a positively charged molecule.

The pigment, called Prussian Blue, sandwiches the drug molecules and holds them in place. (Part of the reason the researchers chose to work with Prussian blue is that the FDA has already found it safe for use in humans.)

WORKING:

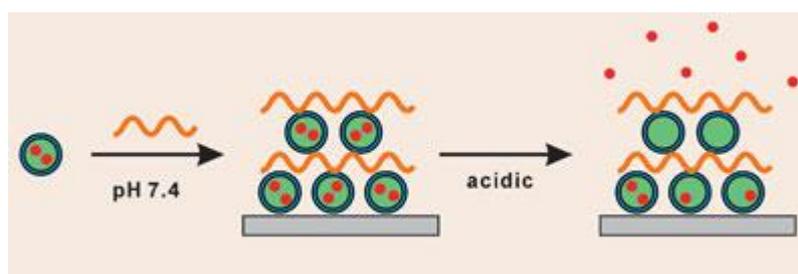
When an electrical potential is applied to the film, the Prussian Blue loses its negative charge, which causes the film to disintegrate, releasing the drugs. The amount of drug delivered and the timing of the dose can be precisely controlled by turning the voltage on and off.

Advantages:

- ❑ The electrical signal can be remotely administered (for example, by a physician) using radio signals or other techniques
- ❑ The films can carry discrete packets of drugs that can be released separately, which could be especially beneficial for chemotherapy.
- ❑ Devices could be designed that can automatically deliver drugs after sensing that they're needed.
- ❑ We could have a signalling system with biosensors.
- ❑ Because the films are built layer by layer, it is easy to control their composition.
- ❑ They can be coated onto a surface of any size or shape, which offers more design flexibility.
- ❑ They are easy to mass-produce using a variety of techniques.

Drawback is that it's hard to coat the drug over a large surface area or over an area that is not planar.

1.5 c) pH RESPONSIVE FILMS



Drug-loaded micelles are trapped between layers of tannic acid to build the multilayer films

The film is created by trapping polymeric spheres in a multilayered surface. To make the spheres they attached a hydrophobic chemotherapeutic agent – e.g. doxorubicin - to a biocompatible polymer using a labile, pH-responsive linker.

On adding a buffer, the drug-loaded polymer forms a suspension of spherical hydrophobic micelles in the aqueous liquid. The micelles are integrated into thin films using a layer-by-layer (LbL) deposition technique.

It is difficult to incorporate hydrophobic species into layers under physiological conditions (pH 7.4) due to their limited functionality. This problem can be overcome by creating a hydrogen-bonded system, using tannic acid. The acid forms hydrogen bonds with the polymeric micelles ensuring that the multilayer remains stable and intact under biological conditions.

The pH-responsive linkers in the micelles can then be used to control drug release from the film when it is required, by changing the pH conditions of the solution surrounding the film.

Future work could look at combining drug-loaded micelles that respond to different chemical or physical triggers, such as redox reactions or light. Their drug release system will be of great interest for localised delivery of cancer therapeutics and vaccines.

1.6 ADVANTAGES

- ❑ The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
 - All tablet dosage forms, softgels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first pass effects. As a result, such formulations often require higher doses and generally have a delayed onset of action.
 - Conversely, buccal and sublingual thin film drug delivery can avoid these issues and yield quicker onsets of action at lower doses.
- ❑ Thin film is more stable, durable and quicker dissolving than other conventional dosage forms.
- ❑ Thin film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain a precise amount of the drug.
- ❑ Thin film not only ensures more accurate administration of drugs but also can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration. These properties are especially beneficial for pediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult.
- ❑ Thin film's ability to dissolve rapidly without the need for water provides an alternative to patients with swallowing disorders and to patients suffering from nausea, such as those patients receiving chemotherapy.
- ❑ Thin film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations.
- ❑ From a commercial perspective thin film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition.

Table 1.	
Special features	Advantages
<ul style="list-style-type: none"> • Thin elegant film • Various sizes and shapes • Unobstructive • Mucoadhesion • Fast disintegration • Quick dissolving • Rapid release 	<ul style="list-style-type: none"> • Convenient dosing • No water needed • No risk of choking • Taste masking • Enhanced stability • Improved patient compliance • Life cycle management

❑ Flexibility in formulation

An inherent benefit is the flexibility of film formulation. A number of physical properties can be altered, including film-dissolution rates, material composition, and API absorption rates.

Customizing dissolution rates

- By combining water-soluble components and additives
- By modifying the combination of film-forming polymers and film thickness (Thickness and mass play an important role.)

Low-MW, water-soluble polymers: rapid disintegration rates

High-MW polymers: good mechanical properties; disintegration time is increased.

- In different physiological conditions (e.g., neutral–alkaline pH).
- Dispersed-phase filler particles can be added to bulk, increase the solids portion to facilitate coating, or alter dissolution rates.
- When distributed throughout the film layer, air or other gases can also change the dissolution time.

1.7 APPLICATIONS

Beyond Immediate release applications:

- **Multilayer drug construction:** two or more layers of API-loaded films could be combined into one format, providing the benefit of layering APIs that would otherwise be incompatible. The layers may be formulated to have the same or various dissolution rates.
- **Topical applications:** the use may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.
- **Binding agents:** could potentially be used to encapsulate a compressed tablet or enclose a multilayer or combination system to enable controlled release of the dose.
- **Buccal, sublingual, and mucosal delivery systems:** dissolvable films may be layered or combined with bioadhesives for these types of oral delivery systems.
- **Gastroretentive dosage systems:** water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.
- **Diagnostic devices:** dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

OTHER APPLICATIONS:

Nanoparticles Incorporated in Bilaminated Films

- NP-Film consisting of carboxylation chitosan-grafted nanoparticles (CCGNs) and bilaminated films, which were composed of the mucoadhesive

chitosan–EDTA hydrogel layer and the hydrophobic ethylcellulose layer, was developed for oral delivery of protein drug.

- ❑ Results showed that the nanoparticles could reversibly open the tight junction of the intestine and inhibit trypsin activity. The release behavior of the nanoparticles from the NP-Film exhibited pH sensitivity.
- ❑ The drug delivery system possessed high mucoadhesive force and low intestinal toxicity.

BREATHE STRIPS

- ❑ Breath strips were created by the company Pfizer.
- ❑ The strips would do the work of a mouthwash in terms of freshening the breath, in a very short time.
- ❑ Through a special formula, a small breath strip that is placed on the tongue nearly instantly dissolves. It creates extreme minty flavor as it does so, which does create fresher breath.
- ❑ Most breath strips are sugar free, so they won't have a negative impact on oral health.
- ❑ They contain chemicals that help fight bacteria, and may actually improve oral health. Breathe strips aren't quite as elegant as presenting mints to guests after dinner.

Oral Quick-Dissolve Strips for Rotavirus Vaccine

- ❑ Rotavirus is a common cause of severe diarrhea and vomiting in children. Rotavirus vaccine is currently produced in a liquid or freeze-dried form.
- ❑ **Disadvantages**(Of Freeze dried form):
 - It must be chilled for transport and storage, making it expensive.
 - In addition, newborns sometimes spit out the liquid, a problem that is less likely to occur with a strip.
- ❑ A thin film was fabricated that should melt quickly in a baby's mouth, prompting the child to swallow the vaccine. The dissolved medication is coated with a material to protect it in the child's stomach.
- ❑ Film is easy to store and transport and would not require refrigeration.

U-Strip Insulin Delivery System

- ❑ It generates ultrasonic transmissions of variable intensity and frequency, which are pulsed through a modified transdermal patch, kinetically motivate the drug contained within the patch.
- ❑ The system postulated that a small, lightweight battery powered ultrasonic transducer could be attached to a transdermal patch.
- ❑ The transducer patch array generates an ultrasonic signal which serves to dilate the skin pores and increase the likelihood of absorption of the large molecular drug through the skin.
- ❑ The U-Strip device can be customized for each patient.

Controlled local delivery of tetracycline with polymer strips in the treatment of periodontitis.

- ❑ The primary purpose of this study was to evaluate the efficacy of tetracycline strips administered singly or in multiples in conjunction with root planning, versus root planning alone, or to an untreated control.
- ❑ Data suggest that multiple strips are superior to a single strip in reducing bleeding on probing, and that local delivery of tetracycline is superior to root planning alone in reducing probing depth.

Nutra3 Complex(R) Develops New fast melting Oral Strips

- ❑ The unique feature of Nutra3 Complex(R) Strip Melts(TM) is that the fast-melting oral strips contain the highest load of active ingredients (250 mg or more per strip) in an oral strip product.
- ❑ This new product provides the nutritional support the body needs to protect against cellular damage from free radicals and promote an anti-aging effect.
- ❑ It contains Trans-Resveratrol, Quercetin and Green Tea and intelligent nutrients (Glutathione, Selenium and SOD) vitamins and minerals, super antioxidants, fiber, lipids and bioflavonoids etc.
- ❑ Advantages: fast-melting and dissolving ,superior bioavailability, great tasting

2. DISKETTES

2.1 INTRODUCTION

Diskette:

It is disk shaped polymeric device containing drug or a circular flat plate made up of drug incorporated polymeric materials.

Diskettes can be used to deliver the drugs by different routes like ophthalmic, transdermal, buccal etc..

They are classified as per their dosage form as shown:

- A) Buccal diskettes
- B) Transdermal diskettes
- C) Ocular inserts

2.2 CLASSIFICATION

2.2 a) BUCCAL DISKETTES

1. Introduction

The buccal mucosa has been investigated for local and systemic delivery of therapeutic agents. The attractive features of delivering drug via buccal route include excellent accessibility and significant robustness of mucosa. The buccal mucosa also provides a delivery route to prevent premature drug degradation within GIT, as well as drug loss due to first-pass hepatic metabolism.

2. Composition

To optimize drug delivery via buccal mucosa, the use of controlled release formulation with mucoadhesive properties is desirable. Several types of polymeric materials have been used in the design of such a system and most of them are hydrophilic macromolecules containing numerous hydrogen-bonding forming groups.

For anionic polymers, Carbopol 934 (CP), sodium carboxymethylcellulose, sodium alginate and maleic anhydride copolymers are often used.

The non-ionic polymers used in such devices are hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose (HPC), polyethylene oxide and polyvinylalcohol; whereas chitosan and diethylaminoethyl dextrin are examples of cationic materials.

Among those bioadhesive polymers, CP is most extensively used and studied. The combination of a non-ionic polymer such as HPC with CP may provide the formulation with a constant drug release rate and desired mucoadhesive properties.

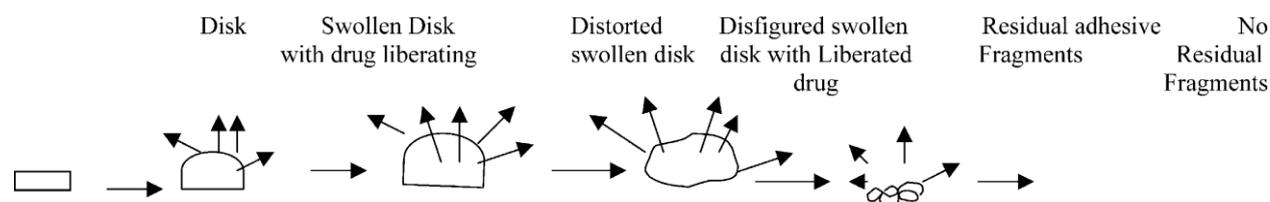
As a result, CP and HPC have been used in several buccal dosage forms to deliver various pharmaceutical agents. In order to adequately control drug release and mucoadhesion of the CP:HPC -based devices, the effects of several variables such as drug solubility and drug loading as well as CP:HPC ratio on drug release and mucoadhesion should be studied in a systematic way.

3. Preparation of buccal disks

Various amounts of CP, HPC and drug were used to prepare different formulations of buccal disks. The CP, HPC and drug were first sieved and mixed homogeneously.

They were compressed by a manual single punch tablet machine (using compression pressure and time 200 kg:cm² and 30 s, respectively.) or using a 13 mm diameter die on an infra-red hydraulic press (using a compression force of 5 tons and a compression time of 15s.).

Approximately 500 ml of ethylcellulose solution (10% w:v in ethanol) was cast on one side of the disks as an impermeable backing layer.



Schematic representation of drug liberation from buccoadhesive disk.

4. Evaluating parameters

- Content uniformity
- In vitro drug release studies
- Mucoadhesion study
- Disk hydration study
- Measurement of bioadhesive strength
- Determination of swelling index and Surface pH of bioadhesive disks
- In vivo evaluation of bioadhesive disks
- Permeation through chicken pouch membrane
- Bioavailability assessment
- In situ release studies
- Microbiological evaluation

5. Examples:

1. Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery
2. Formulation and evaluation of Diclofenac Sodium buccoadhesive disks
3. Diskettes of mucoadhesive polymeric nanoparticles for oral (buccal) transmucosal delivery of Fluoxetine hydrochloride

2.2 b) TRANSDERMAL DISKETTES

1. Introduction

Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transdermal disks etc. emerged.

2. Formulation

The common ingredients which are used for the preparation of TDDS are as follows.

- 1) **Drug:** Drug is in direct contact with release liner.

Ex: Nitroglycerin, Methotrexate and Estrogen etc.

2) **Linners:** Protects the patch during storage.

Ex: polyester film.

3) **Adhesive:** Serves to adhere the patch to the skin for systemic delivery of drug.

Ex: Acrylates, Polyisobutylene, Silicones.

4) **Permeation enhancers:** Controls the Release of the drug.

Ex: Terpenes, Terpenoids, Pyrrolidones.

Solvents like alcohol, Ethanol, Methanol.

Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

5) **Backing layer:** Protect patch from outer environment.

Ex: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.

3. Evaluation parameters

- Interaction studies
- Thickness of the patch
- Weight uniformity
- Folding endurance
- Percentage Moisture content
- Percentage Moisture uptake
- Water vapour permeability (WVP) evaluation
- Drug content
- Uniformity of dosage unit test
- Polariscope examination
- Shear Adhesion test
- Peel Adhesion test
- Thumb tack test
- Flatness test
- Percentage Elongation break test
- Rolling ball tack test
- Quick Stick (peel-tack) test
- Probe Tack test
- *In vitro* drug release studies
- *In vitro* skin permeation studies
- Skin Irritation study and Stability studies

4. Examples

Transdermal discs of nitroglycerin, Primaquine transdermal patches

2.2 c) OCULAR INSERTS

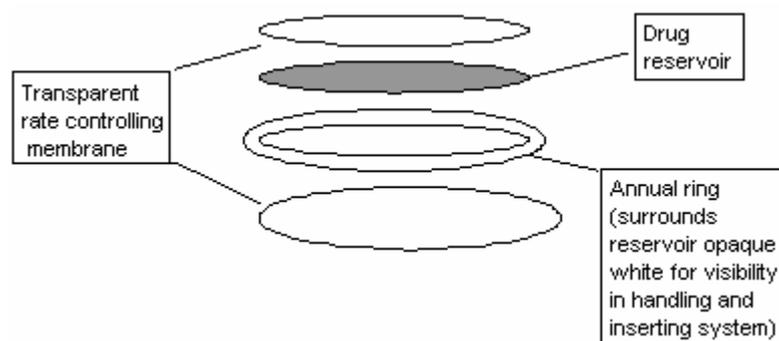
1. Introduction

In order to overcome the constraints placed by conventional ocular therapies viz. Short residence time, Pulsed dosing of drug.,Frequent instillation, Large drainage factor. Newer ocular drug delivery systems are being explored to develop extended duration and controlled release strategy.

Some of the newer, sensitive and successful ocular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

The following are ocular diskettes in existence:

- a) Membrane-bound ocular inserts (biodegradable and non-biodegradable)
e.g. Ocusert®, Alza Corp.
- b) Collagen shields
- c) ophthalmic rods (artificial tear inserts e.g. Lacrisert®)
- d) Soft contact lenses etc...



Schematic diagram of ophthalmic insert

2. Classification of Ocular Inserts:

(Based upon their solubility behaviour)

- 1) Insoluble inserts
 - a) Diffusion based
 - b) Osmotic based
 - c) Soft contact lenses
- 2) Soluble inserts
- 3) Bioerodible inserts

3. Composition

Table 1: Components of diffusional inserts.

Central reservoir	Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, poly (vinylpyrrolidone), polyoxethylene stearate.
Micropores membrane	Polycarbonates, polyvinyl chloride, polysulfones, cellulose esters, crosslinked poly (ethyl oxide), cross-linked polyvinylpyrrolidone, and cross-linked polyvinyl alcohol.

Table 2: Components of osmotic inserts.

Water permeable matrix	Ethylene - vinyl esters copolymers, Divers- plasticized polyvinyl chloride (PVC), polyethylene, cross-linked polyvinylpyrrolidone(PVP)
Semi permeable membrane	Cellulose acetate derivatives, Divers – Ethyl vinyl acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit [®]).
Osmotic agents	Inorganic – magnesium sulfate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulfate. Organic- calcium lactate, magnesium succinate and tartaric acid. Carbohydrates – Sorbitol, mannitol, glucose and sucrose.

Table 3: Components of Soluble Inserts

Soluble synthetic polymers	Cellulose derivatives – Hydroxypropyl cellulose methylcellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Divers – Polyvinyl alcohol, ethylene vinyl acetate copolymer.
Additives	Plastisizer – Polyethylene glycol, glycerin, propylene glycol Enteric coated polymer – Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate. Complexing agent – Polyvinyl pyrrolidone. Bioadhesives – Polyacrylic acids.

4. SOFT CONTACT LENSES

1. Introduction

These are shaped structure made up of a covalently crosslinked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components.

When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture²⁹ or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems.

2. Types of contact lenses

- By Functions
 - Corrective contact lenses
 - Cosmetic contact lenses
 - Therapeutic contact lenses
- By constructional material
- By wear time
- By frequency of replacement
- By design
- Implantable

3. Construction materials:

- The first contact lenses were made of glass, which caused eye irritation, and were not wearable for extended periods of time. But when lenses were made from polymethyl methacrylate (PMMA or Perspex/Plexiglas), contacts became much more convenient. These PMMA lenses are commonly referred to as "hard" lenses. These polymers are referred as RGP(Rigid Gas Permeable) materials.
- The first soft (hydrogel) lenses ('Soflens') contains material (polymacon).
- In 1999, 'silicone hydrogels' became available. Silicone hydrogels have both the extremely high oxygen permeability of silicone and the comfort and clinical performance of the conventional hydrogels. While it provides the oxygen permeability, the silicone also makes the lens surface highly hydrophobic and less "wetable." This frequently results in discomfort and dryness during lens wear. In order to compensate for the hydrophobicity, hydrogels are added (hence the name "silicone hydrogels") to make the lenses more hydrophilic.

4. Manufacturing of contact lenses

Most contact lenses are mass produced.

- **Spin-cast lenses** - A spin cast lens is a soft contact lens manufactured by whirling liquid silicone in a revolving mold at high speed.
- **Lathe turned** - A lathe turned contact lens is cut and polished on a CNC [lathe](#). The lens starts out as a cylindrical disk held in the jaws of the lathe. The lathe is equipped with an industrial grade [diamond](#) as the cutting tool. The CNC Lathe turns at nearly 6000 RPM (revolutions per minute) as the cutter removes the desired amount of material from the inside of the lens. The [concave](#) (inner) surface of the lens is then polished with some fine abrasive paste, oil, and a small polyester cottonball turned at high speeds. In order to hold the delicate lens in reverse manner, wax is used as an adhesive. The [convex](#) (outer) surface of the lens is thus cut and polished by the same process.
- **Molded** - Moulding is used to manufacture some brands of soft contact lenses. Rotating moulds are used and the molten material is added and

shaped by centrifugal forces. Injection moulding and computer control are also used to create nearly perfect lenses.

- **Hybrids**

5. Examples

Although many companies make contact lenses, in the US there are four major manufacturers:

- Acuvue/Vistakon (Johnson & Johnson)
- Ciba Vision (Novartis)
- Bausch & Lomb
- CooperVision

REFERENCES:

- ❑ Wikipedia, The Encyclopedia
- ❑ S.B. Borsadia et al., "Quick-Dissolving Films—A Novel Approach to Drug Delivery," *Drug Delivery Technol.* **3** (3), 63–66 (2003).
- ❑ P. Frey, "Film Strips and Pharmaceuticals," *Pharma. Mfg. & Packag. Sourcer*, Winter, 92–93 (2006).
- ❑ "Oral Thin Films," in *Orally Disintegrating Tablet and Film Technologies*, 4th ed. (Technology Catalysts International, Falls Church, VA, 2006), 18–31.
- ❑ S.D. Barnhart and M.S. Sloboda, "The Future of Dissolvable Films," *Drug Delivery Technol.* **7** (8), 34–37 (2007).
- ❑ S.D. Barnhart, "Thin Film Oral Dosage Forms," in *Modified Release Drug Delivery Technology*, 2nd ed., Vol. 1, in press (Informa Healthcare; New York, NY, 2008) 209-216.
- ❑ Hydrogen-bonded multilayer of pH-responsive polymeric micelles with tannic acid for surface drug delivery Byeong-Su Kim, Hyung-il Lee, Yunhong Min, Zhiyong Poon and Paula T. Hammond, *Chem. Commun.*, 2009, 4194
- ❑ <http://www.faqs.org/patents>
- ❑ PMID: 11846194 [PubMed - indexed for MEDLINE]
- ❑ www.pharmainfo.net
- ❑ International Journal of ChemTech Research, CODEN(USA): IJCRGG ISSN : 0974-4290 Vol.2, No.1, pp 576-583, Jan-Mar 2010
- ❑ www.sciencedirect.com
- ❑ International Journal of Pharmaceutics 177 (1999) 201–209.

PREVIOUS QUESTIONS

1. What is diskette? Classify them and discuss in brief the methods to evaluate them.
2. Compare films/strips with TDDS; write an idea about modified TDDS.
3. Define diskettes. Write a note on buccal diskettes.