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Mouth Dissolving Film: A Review

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ABSTRACT

Mouth Dissolvable films (MDFs) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. MDF which disintegrate or dissolve within 1min when placed in the mouth without drinking water or chewing. Also, used for the taste masking of widely bitter tasted drugs which are most important for the paediatric patients. These drug delivery systems allow the medication to bypass the first pass metabolism thereby making the medication more bio available. Formulation of oral films involves the application of both aesthetic and performance characteristics such as plasticized hydrocolloids, active pharmaceutical ingredient, taste masking agent being laminated by solvent casting or hot melt extrusion. Solvent casting being the most preferred offers great uniformity of thickness and films have fine gloss and better physical properties. Oral strips are evaluated for various attributes such as thickness, Surface pH, folding endurance, disintegration and dissolution study. This review describes about the formulation methodology, evaluation parameter.

KEYWORDS

Mouth Dissolving Film, Solvent Casting, Semisolid Casting, Bitter Taste Masking.

INTRODUCTION

Mouth dissolving films 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 is 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. MDFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices[1]. MDFs 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[2].

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Fast-dissolving dosage technologies are important for patients who have difficulty taking traditional oral dosage forms, as well as those who want the convenience of any-time dosage when water is not available.

Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. The most common complaint was tablet size, followed by larger surface area and taste. For the last two decades, there has been increase use of more patient-compliant dosage forms[3].

Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolve/disintegrate in the mouth within few seconds without water and eliminates the fear of chocking as an alternative to fast dissolving tablets. Basically the fast dissolving film can be considered as an ultra thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. Most fast

dissolving films are having taste masked active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipients.[4, 5]

These films generally dissolve within seconds to release the active agents but can be modified to release the drug more slowly depending upon film thickness and selection of the polymer matrix. A film or strip can be defined as a dosage form that employs water. Dissolving polymer which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or in the oral cavity to provide rapid local or systemic drug delivery. Zengen Inc developed this new delivery technology, which is a medicated oral strip structured as a proprietary bilayer system. These films typically contain water soluble hydrocolloids such as HPMC, pullulan, pectin, carboxymethyl cellulose, an effective dose of active agent, other additives such as flavouring agents, plasticizers and preservatives. The disintegration and dissolution characteristic of thin film is dependent on thickness and combination of hydrocolloids.[6,7]

These four tastes are located on different receptors on tongue, sensations for sweet are located at tip of the tongue and sensations for sour are located at sides of the tongue whereas bitterness at the back of the tongue and salty sensations are located at the sides and tip of the tongue [8]. Recently, a basic taste umami has been discovered. Umami is the fifth independent taste produced by monosodium glutamate (MSG) contained mainly in seaweed and disodium inosinate (IMP) in meat and fish. These above taste receptors that bind to molecules down by saliva transmit electrical impulses by 7th, 9th and 10th cranial nerves to these areas of brain which participate in perception of taste.

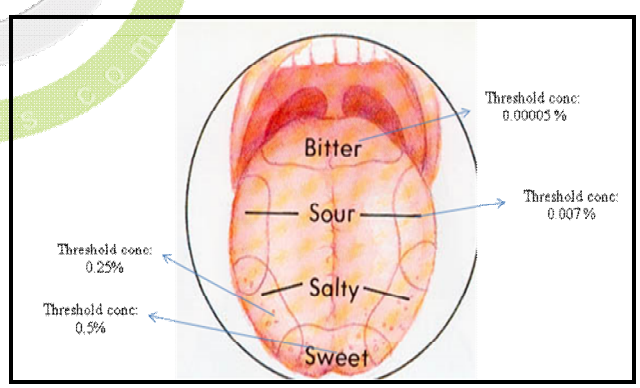
Among various approaches two are commonly used to diminish the bitter taste of drug. [9]

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).

2. By altering the affinity and nature of drug which will interact with the taste receptor.

The Rapidly dissolving film are essentially prepared using water soluble and fast disintegrating polymers which also possess good film forming properties like hydroxypropyl methylcellulose (HPMC), Pullulan, polyethylene oxide (PEO), polyvinyl pyrolidone (PVP) and hydroxypropylcellulose (HPC).[10,11] Although HPMC is more commonly used for RDF formation, Pullulan is also often used as a film former due to its excellent film forming property. Pullulan is a natural polysaccharide produced from starch by cultivating black yeast Aureobasidium Pullulan. It is a white, tasteless, odourless water soluble powder. Pullulan PI-20 grade is the deionised form of Pullulan having an average molecular weight of 2,00,000 Daltons . RDF using Pullulan can be manufactured using solvent casting, hot melt extrusion or compression moulding. Solvent casting is the most common and traditional method .[12]

(F—25)Threshold for taste is a minimum conc. Of a substance that evokes perception of taste .It is observed that tounge is 10,000 times more sensitive to the bitterness of quinine than to sweetness of sugar.



Taste buds are onion-shaped structures containing between 50 to 100 taste cells.[13] Chemicals from food or oral ingested mendicants are dissolved by the saliva and enter via the taste pore. There they either interact with surface proteins known as taste receptors or with pore-like proteins called ion channels. These interactions cause electrical changes within the taste cells that trigger them to send chemical signals that translate into neurotransmission to the brain. Salt and sour

responses are of the ion channel type of responses, while sweet and bitter are surface protein responses. The electrical responses that send the signal to the brain are a result of a varying concentration of charged atoms or ions within the taste cell. These cells normally have a net negative charge. Tastants alter this state by using varying means to increase the concentration of positive ions within the taste cell. This depolarization causes the taste cells to release neurotransmitters, prompting neurons connected to the taste cells to relay electrical messages to the brain.[14] In the case of bitter taste, such as quinine, stimuli act by binding to G-protein coupled receptors on the surface of the taste cell. This then prompts the protein subunits of alpha, beta, and gamma to split and activate a nearby enzyme. This enzyme then converts a precursor within the cell into a "second messenger." The second messenger causes the release of calcium ions (Ca++) from the endoplasmic reticulum of the taste cell. The resulting build-up of calcium ions within the cell leads to depolarization and neurotransmitter release. The signal now sent to the brain is interpreted as a bitter taste.

Ideal Characteristics of a Suitable Drug Candidate[15, 16]

- The drug should have pleasant taste.
- Dose should be low as possible.
- The drugs with smaller and moderate molecular weight are preferable.
- Good stability in water and saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Benefits of Oral Thin Films[17]

- Larger surface area promotes rapid disintegration and dissolution in the oral cavity. Oral films are flexible and thus less fragile as compared to ODTs.
- Consumer handling and storage.
- Ease of swallowing and no need of water have led to better acceptability amongst the dysphagic patients.
- Dosage form can be consumed at any place and anytime as per convenience of the individual.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism.
- Enhanced oral bioavailability of molecules that undergo first pass effect. 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.

Composition of the System

1) Drugs

Several class of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics(cetrigine), NSAID'S (e.g. paracetamol, diclofenac meloxicam, valdecoxib).Chlorpheniramine maleate(Anti-allergic), Zolmitriptan.

Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in the OS[18].

2) Water Soluble Polymers[19, 20, 21]

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. 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, carboxmethylcellulose cekol 30,

Polyvinylpyrollidone PVP K-90, Pectin, Gelatine, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrin and eudragit-RD.Polymerized rosin is a novel film forming polymer.

Pullulan is obtained from natural origin, so does not require chemical modification.

Polymer should be:

- Non toxic, non incompatible and devoid of leachable impurities.
- Good wetting and spreading property.

3) Plasticizers

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of films. The mechanical properties such as

1) Tensile strength and
2) Elongation to the films has also been improved by the addition of plasticizers.

- Used in 1-20 %w/w of the dry polymer weigh. Their concentration may affect these properties. The commonly used plasticizers are glycerol, dimethyl, diethyl and di-butylpthalate, citrate derivatives such as tributyl, triethyl citrate, polyethylene glycol, and castor oil, etc21.
- Various study carried out in different plasticizer to study their effect on gelatine strips which results observed that malic acid was found to better plasticizer when compared to citric acid, Oleic acid and tartaric acid as it was not crystallize out when the film was dried.
- Low molecular weight of polyethylene glycol was found to better plasticizer than high M.W polyethylene glycol.
- Maltodextrin can also be plasticized and converted into oral dissolving film with incorporation of glycerine and propylene glycol as plasticizer in the concentration range of 16–20%w/w, and found to be more advantageous by using glycerine over propylene glycol as it shows miscibility problems with maltodextrin either by using solvent casting or hot melt extrusion methods. [22,23,24]

4) Saliva Stimulating Agents

The saliva stimulating agents are enhance, production of saliva that would aid in the faster disintegration of the rapid dissolving film formulations and utilized as salivary stimulants. Citric acid, malic acid, ascorbic acid and tartaric acid are the considered as the salivary stimulants, citric acid being the most preferred amongst them. These agents are used in combination between 2 to 6%w/w of weight of the strip. Sweeteners are also act as salivary stimulants.[25]

5) 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 sulphate, benzalkonium chloride, bezthonium chloride, tweens etc. Most important surfactant is polaxamer407 that is used as solubilizing, wetting and dispersing agent.[26, 27]

6) Flavour

Any flavour can be added, such as intense mints, sour fruit flavours or sweet confectionery flavours.[28, 29]

(A) Flavours

Natural Flavours

Juices - Raspberry

Extracts - Liquorices

Spirits - Lemon & Orange

Syrups – Blackcurrant

Tinctures -Ginger

Aromatic waters - Anise & Cinnamon

Aromatic Oils – Peppermint & Lemon.

Synthetic Flavours

Alcoholic solutions

Aqueous solutions

Powders

Natural Vs Synthetic

Cheaper

More readily available

Fewer variables in chemical composition

More stable

Basis of Choosing Flavours

Complementary to existing flavour of the drug.

Known popularity of particular flavours.

Age of patients.

Allergy.

Table 1: Flavouring agents for taste masking

Basic Taste	Masking agents
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry.
Sour	Citrus flavor, licorice, root beer, raspberry.

Anethole effectively masked bitter taste as well as the after taste of zinc, which is used in treating the common cold.

(B) Sweeteners

Complement flavours associated with sweeteners.

Soothing effect on the membranes of the throat due to salivary stimulating agents.

Natural Sweetener

Sucrose, glucose, fructose

Sorbitol, mannitol, glycerol

Honey, liquorice

Artificial Sweetener

Saccharin, Saccharin sodium

Aspartame

Nutritive: Sucrose, Fructose and Glucose

Polyols: Mannitol, Sorbitol, Xylitol, Erythritol, Maltitol.

Non-Nutritive: Aspartame, Sucralose, Neotame and Saccharine

Novel sweeteners: Trehalose, Tagatose.

Table 2: List of FDA approved Non-Nutritive Sweeteners (Sweetness factor, Sucrose = 1)

Sr. No.	Sweetener	Sweetness Factor
1	Aspartem	180-200
2	Sucralose	600
3	Acesulfame K	200
4	Neotame	7000-13000
5	Saccharin	300

7) Colour

A full range of colours is available, including FD&C colours, EU Colours, Natural Colours. 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.

Manufacturing Methods

i) Solvent casting.

ii) Semisolid casting.

iii) Hot melt extrusion.

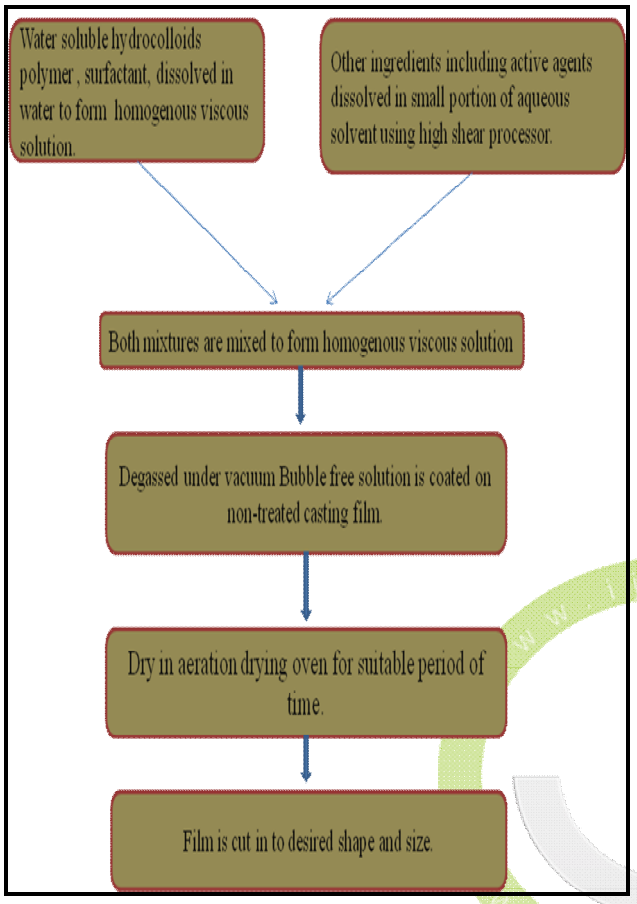
iv) Solid dispersion extrusion.

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, 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 (HME)[30]

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.

Advantages of hot melt extrusion for film formation include-

- No requirement on the compressibility of the active ingredients.
- More uniform dispersion of the fine particles due to intense mixing and agitation causing suspended drug particles to deaggregate in the molten Polymer.
- The bioavailability of the drug substance could be improved when it is dispersed at the molecular level in hot melt extruded dosage forms.

Producing thin films for transdermal /transmucosal drug delivery and wound care is via film casting from aqueous or organic solvents. The hot melt extrusion process has recently gained acceptance in the pharmaceutical industry. Building on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers, and plasticizers into various final forms to achieve desired drug release profiles. The benefits of using HME over traditional processing techniques include:

- Fewer unit operations
- Better content uniformity
- An anhydrous process
- A dispersion mechanism for poorly soluble drugs
- A low energy alternative to high-shear granulation
- Less processing time compared with conventional wet granulation.

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.

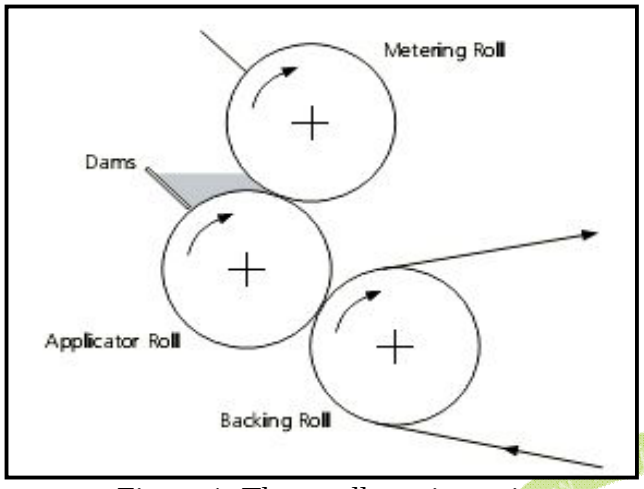


Figure 1: Three roll coating unit

6) Using Ion Exchange Resin[31, 32, 33]

Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. Ion exchange resins contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger. They are further classified as inorganic and organic resins. Due to high molecular weight, they are not absorbed by the body which makes them safe for human use. The most frequently employed polymeric network is a copolymer of styrene and divinylbenzene. Ion exchange resins are used in formulations for stabilization of sensitive components, sustained release of drugs, providing tablet disintegration and taste masking. Drug resin complex dissociation does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odour of the drug . Tulsion 335 is a weak acid cation exchange polyacrylic resin with carboxylic acid as a functional group. It possesses good taste masking ability and is supplied in a powder form.

E.g. Amberlite™ Irp64, Amberlite™ Irp69, and Amberlite™ Irp88.

In another study, an attempt has been made to mask the bitter taste of roxithromycin by complexation technique. Weak cation exchange resins Indion 214 and Amberlite IRP64, polymer carbopol 934P were used in formulation of complexes with the drug. Amberlite IRP64 was found to be better complexing agent for masking the bitter taste of roxithromycin.

Evaluation of Oral Thin Strip

Appearance

All prepared films were checked for their appearances either they are transparent or opaque.

Weight Variation

All batches were evaluated for its weight variation and thickness. Weight variation is evaluated by using electronic balance and Avg. weigh is calculated.

Thickness

Thickness of the prepared film was measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

Mechanical Properties[34, 35, 36]

Mechanical properties like Tensile Strength, % Elongation, and Folding Endurance were evaluated:

Tensile Strength

It was measured using Tensiometer. The films of size 2×2 cm^2 and free of physical imperfections were placed between two clamps held 10 mm apart. The films were to be pulled by clamp at a rate of 5mm/min.

Tensile strength =Load at failure × 100/ Strip thickness × Strip width

Percentage Elongation

It was calculated by measuring the increase in length of the film after tensile measurement by using the following formulae.

Percent Elongation = [L-L0] X 100 / L0

Where L was the Final length and L0 was initial length.

Folding Endurance

It was measured by folding the film at the same place repeatedly until a visible crack is observed. This gives an indication of brittleness of the film.

Surface pH

The films were allowed to swell in closed petridish at room temperature for 30 minutes in 1 mL of distilled water. Solution was placed under digital pH meter to determine the surface pH.

Disintegration Time[37, 38]

Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The require size of film (2×2 cm2) was placed in a stainless steel wire mesh containing 25 mL of pH 6.8 simulated salivary fluid. Time taken by film to break and dissolve was measured as in-vitro disintegration time and invitro dissolution time.

***In-vitro* Dissolution Studies**[39, 40, 41]

An in-vitro dissolution study for all the batches was performed for five minutes and each film was placed with the help of forceps in a 50 mL glass beaker containing 30 mL of simulated salivary fluid pH 6.8 Dissolution medium was kept at 37º C ± 0.5 º C and magnetic stirrer was rotated at 50 rpm.

The samples (5 mL) was withdrawn at 15 second, 30 seconds, 1, 2, 3, 4, 5 min and replaced with fresh simulated salivary fluid pH 6.8.

The samples were analyzed for the drug released using UV-Visible spectrophotometer.

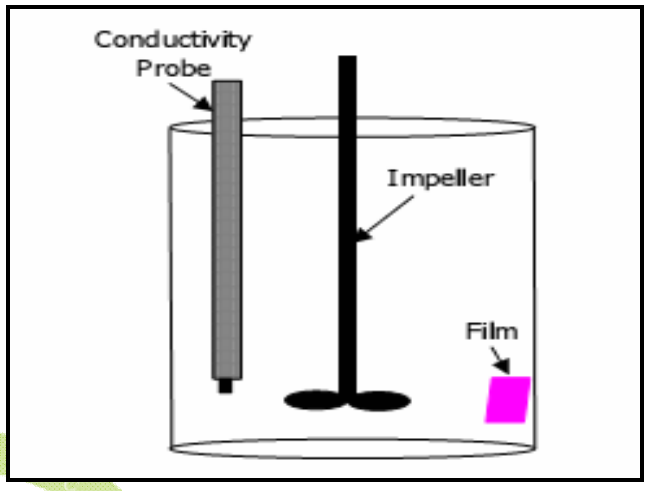


Figure 2: Diagram of equipment set-up

Packaging

A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. APR-Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually. [42]

Table 3: List of marketed films containing Active Pharmaceutical Ingredient:[43]

Product	Company	API	Use
Benadryl	Pfizer	Diphenylhydramine	Cough and allergy
Listerine pocketpak	Pfizer	Menthol	Mouth freshener
Orafilm	Apothecus	Benzocaine	Pain relieving strips
Spiderman	Aquafilm	Vitamin	Vitamin suppliment
Theraflu	Novartis	Diphenhydramine HCl	Cough suppressant
Triaminic	Novartis	Dextromethorphan	Cold/allergy
Sudafed	Pfizer	Phenylephrine	Nasal decongestant

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