

**OVERVIEW ON ORAL STRIP**

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ABSTRACT

Oral films 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 for delivering vitamins and personal care products. Oral drug delivery system is the successful delivery of the drug to the body; offer a convenient way of dosing medications. Oral dissolving film Technology (ODFTS) that can be administrated in the oral cavity for a shorter period of time with quick onset of action, which enhance the therapeutic action of drug. The methodologies used in the development of oral strip for pediatric and geriatric patient's population, who are difficulty in swallowing larger dosage forms. ODFT offers an alternate platform for molecules that undergoes first pass metabolism. Our review article suggests that oral film can be the possible way to improve patient compliance and robustness.

KEY WORDS: Oral film, Solvent casting, Semisolid casting, hydrophilic polymer, Disintegration time.

INTRODUCTION:**OVERVIEW OF FAST DISSOLVING DOSAGE FORM:**

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating¹ and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. The novel technologies of oral fast-dispersing dosage forms are also known as fast dissolve rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition "a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water is known as an oral fast-dispersing dosage form". Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules.² an estimated 35% of the general population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer

from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, surface, form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.³⁻⁵

CURRENT ORAL FAST-DISPERSING DOSAGE FORM TECHNOLOGIES:

Several methods are employed in the preparation of oral fast-dispersing tablets, such as modified tableting systems, floss, or Shearform™ formation by application of centrifugal force and controlled temperature, and freeze drying.

For ease of description, fast-dissolve technologies can be divided in to three broad groups:

- (A) Lyophilized systems,
- (B) Compressed tablet-based systems,
- (C) Thin film strips/Fast dissolving films (FDFs).

A) THE LYOPHILIZED SYSTEMS:

This system has been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units

have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems.

B). COMPRESSED TABLET-BASED SYSTEMS:

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard HDPE bottles or blisters through to more specialists pack designs for product protection, e.g. CIMA Labs'- PackSolv. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or super- disintegrants or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail"s Fuisz technology. It uses the proprietary Shear form system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms.^{6,7}

C) THIN FILM STRIPS/FAST DISSOLVING FILMS (FDFS):

Oral films, also called oral wafers in the related

literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) 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 for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs.⁸ This is largely as a result of the success of the consumer breath freshener products such as Listerine PocketPaks in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats.⁹

➤ **COMPOSITION CONTAINS THE FOLLOWING:**

- Drug 1-25%
- Water soluble polymer 40-50%
- Plasticizers 0-20%
- Fillers, colours, flavours etc. 0-40%

CLASSIFICATION OF ORAL FILM:

There are three different subtypes:
 (1) Flash release,
 (2) Mucoadhesive melt-away wafer,
 (3) Mucoadhesive sustained-release wafers.
 These three types of oral films are differentiated from each other in following table-1.

Table 1: Types of Wafers/oral Film and their properties:¹⁰

Sub Type/ Property	Flash release wafer	Mucoadhesive melt-away wafer	Mucoadhesive sustained release wafer
Area (cm ²)	2-8	2-7	2-4
Thickness(μm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer System	Multi-layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid

			solution
Application	Tongue (upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 Hours.

ADVANTAGES OF ORAL THIN FILM:

This dosage form enjoys some distinct advantages over other oral formulations such as:

- Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
- The disadvantage of most ODT is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.
- As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
- Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices¹¹
- The oral or buccal mucosa being highly vascularised, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
- Patients suffering from dysphagia, repeated emesis, motion sickness and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
- OTFs are typically the size of a postage stamp and disintegrate on a patients tongue in a matter of seconds for the rapid release of one or more APIs. The formulation of dissolvable films is customarily facilitated through aqueous polymer matrices that span a wide molecular weight (MW) range, thereby providing flexibility to achieve certain physical properties.

DISADVANTAGE OF ORAL STRIP:

The disadvantage of OS is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active

can be improved up to 50% per dose weight¹². There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly limits the range of compatible drug products. The other technical challenge with these dosage forms is achieving Dose Uniformity¹³

➤ **MANUFACTURING OF RAPIDLY DISSOLVING FILM:**

One or a combination of the following processes may be used to manufacture the RDF¹⁴

- Hot-melt extrusion
- Solid dispersion extrusion
- Rolling
- Semi-solid casting
- Solvent coating

a) SOLVENT CASTING METHOD :

The current most preferred manufacturing process for fabricating RDF is the solvent casting. In this method, water-soluble hydrocolloids are completely dissolved in water in a mixing tank to form a homogenous viscous solution. Other ingredients, including active agents, are dissolved in small portions of the aqueous solvent using a high-shear processor. The active mixture is then added to the viscous hydrocolloid solution to form a homogenous viscous solution. This viscous solution is degassed under vacuum. The resulting bubble-free solution is coated on a non-treated casting film with a typical coating thickness of 5 to 20ml. (1 mil= 25.4 μm) The coated film is subsequently sent into an aeration-drying oven. The dry film is then cut into the desired shape and size for the intended application.

Polymers used to prepare quick dissolving films include Hydroxypropylmethyl cellulose (HPMC), Hydroxypropyl cellulose (HPC), pullulan, sodium alginate, pectin, Carboxy methyl cellulose (CMC) and polyvinyl alcohol (PVA). By carefully balancing the mechanical properties, solubility rate, taste and mouth feel for the film strip, these polymers can be employed to design quick dissolve strips. By controlling the molecular weight

distribution (MWD) of the film matrix, the properties can be optimized. Usually when designing quick dissolve strips, a polymer with low MWD or viscosity such as HPMC E5 or pullulan PI-20 is employed. When the desired physical properties are not obtained using a single low viscosity polymer, mixing various grades of polymers may overcome this problem. When mixing a high viscosity polymer with low viscosity polymer, the quick-dissolve strip will generally have mechanical properties similar to high molecular weight polymer and the solubility rate will be similar to the low molecular weight polymer^{14,15}

b) HOT MELT EXTRUSION (HME) :¹⁶⁻¹⁸

This method is commonly used to prepare granules, sustained release tablets; transdermal and transmucosal drug delivery system. Processing films by this technique,

involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting technique.

Advantages of hot melt extrusion for film formation include-

- Neither solvent nor water is used in the process
- Fewer processing steps are needed; time consuming drying steps are eliminated.
- 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.

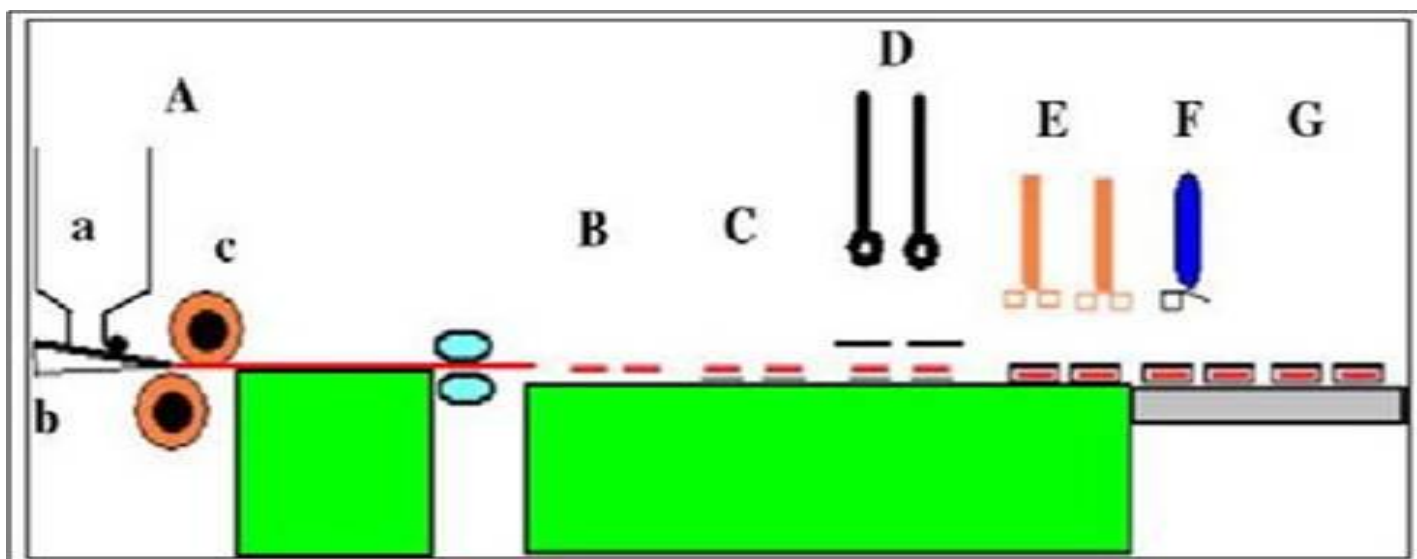


Figure 1: Schematic representation of a Typical OST Manufacturing unit.

The equipment used for hot melt extrusion consists of extruder, downstream auxiliary equipment and monitoring tools. Extruder is composed of a feeding hopper, barrel, screw, die, screw-driving unit and heating/cooling device. Producing thin films for transdermal /transmucosal drug delivery and wound care is via film casting from aqueous or organic solvents. Repka et al studied the influence of Chlorpheniramine maleate on topical HPC films by hot melt extrusion technique. Chlorpheniramine has been reported to function as an effective plasticizer, increasing percent elongation and decreasing tensile strength in concentration dependent manner. Chlorpheniramine also acted as a processing aid in the extrusion of hot melt films and allowing film processing at lower temperature.

The HME 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

A few challenges in the formulation of RDF are that in order to maintain its fast dissolving characteristics, the thickness of the film should be carefully controlled. Therefore, its drug loading capability is limited. Overcoming the unwanted taste of certain active ingredients can be a challenge to the

formulator. The extent of these challenges depends on the size of the dose; the desired release profile and desired absorption kinetics. Although these products offer increased convenience, as with every medication there are certain dangers. It has been reported that those patients taking diphenylhydramine containing products should be counselled regarding the drowsiness effects it is likely to produce and cautioned about driving. Since patients will now be able to carry the medication with them at all times and these products resemble similar dosage form i.e. breath fresheners, patient may be tempted to go above and beyond normal recommended dose. Patient should be counselled not only regarding possible side effects, but also cautioned about using the product incorrectly.¹⁹⁻²³

c) SOLID DISPERSION EXTRUSION METHOD:

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

d) ROLLING METHOD:

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water, mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and sizes.

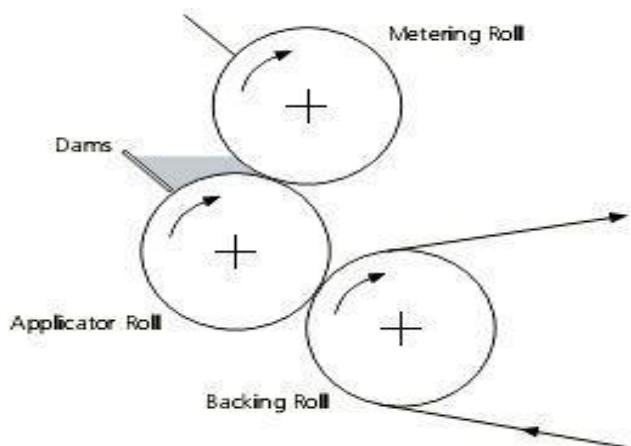


Figure 2: Three roll coating unit

TECHNOLOGIES:²⁵⁻²⁷

Soluleaves™ technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. Soluleaves™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules.

The delivery system can be used for the cough/cold, gastrointestinal pain areas as well as delivering nutritional products. Soluleaves™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

FEATURES OF SOLULEAVES™:

- A vegetable based polymer film that carries low levels of active ingredients and flavouring agent
- Fast dissolution in the mouth
- Enhanced taste masking
- Enhanced convenience, portability and discreet format
- Sugar free variant suitable for diabetics
- Aqueous based and solvent free
- Application in a range of vitamins, flavourings, and pharmaceutical actives
- Suitable for paediatric and geriatric patients
- The SoluLeaves™ system is patented

Wafertab™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible film strip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The wafertab™ film strip can be flavoured for additionally improved taste masking. The active ingredient 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 wafertab™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. Wafertab™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release, or for use by patients who have difficulty swallowing.

FEATURES OF WAFERTAB™:

- Very stable format, fast dissolving oral film
- Enhanced taste masking
- Enhanced convenience, portability and discreet format
- Sugar free variant suitable for diabetics
- Aqueous based and solvent free
- Applications in unstable pharmaceutical forms, particularly salt forms.
- The WaferTab™ system is uniquely patented²⁸

Xgel™ film is at the heart of meldex international's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. Xgel™ film provides unique product benefits for healthcare and

pharmaceutical products: it is nonanimal derived, approved on religious grounds and is suitable for vegetarians; the film is continuous production processing provides an economic and competitive manufacturing platform. Xgel™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The xgel™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. Xgel™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use. All of the Xgel ingredients are well known and generally regarded as safe (GRAS).²⁹⁻³²

Foamburst™ is a special variant of the soluleaves™ technology where an inert gas is passed into the film during production. This results in a film with a honey combed structure, which dissolves rapidly giving a novel mouth sensation. Foamburst™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.³³

EVALUATION OF ORAL THIN STRIP:³⁴⁻³⁹

➤ **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.

➤ **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**

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

a) Tensile strength

It was measured using Tensio meter (Ponco Machines Ahmedabad). The films of size 2x2 cm² 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

b) PERCENTAGE ELONGATION:

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

Percent Elongation = $[L-L_0] \times 100 / L_0$

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

c) 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:**

Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The require size of film (2x2 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:**

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 37^o C ± 0.5 ^o C and magnetic stirrer was rotated at 50 rpm. The samples (2 mL) was withdrawn at diff. Time interval and replaced with fresh simulated salivary fluid pH 6.8. The samples were analyzed for the drug released using UV-VIS spectrophotometer.

➤ **TASTE EVALUATION:**

If drug is bitter then taste acceptability was measured by a taste panel with 5 mg drug and subsequently 5- mg film sample held in the mouth for 5–10 s, then spat out, and the bitterness level was recorded. Volunteers were asked to gargle with distilled water between the drug and sample administration. The following scale was used:

+ = very bitter

++ = moderately bitter

+++ = slightly bitter

++++ = tasteless or taste-masked.

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.

Table 2: List of marketed films containing Active Pharmaceutical Ingredient (API) ⁴⁰

Product	Company	API	Use
Orafilm	Apothecus	Benzocaine	Pain relieving strips
Chloraseptic relief strips	Zengen	Benzocain	Local anaesthetic,Pain relief
Triaminic	Novartis	Dextromethorphan	Cold/allergy
Theraflu	Novartis	Diphenhydramine HCl	Cough suppressant
Spiderman	Aquafilm	Vitamin	Vitamin supplement
Sudafed	Pfizer	Phenylephrine	Nasal decongestant
Listerine	Pfizer	Menthol	Mouth freshener
Orafilm	Apothecus	Benzocaine	Pain relieving strips
Benadryl	Pfizer	Diphenylhydramine	Cough and allergy

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