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FAST DISSOLVING ORAL FILMS: AN INNOVATIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Among the different oral drug delivery systems the fast dissolving oral films (FDOFs)is rapidly gaining interest in pharmaceutical industry. This is the most advanced form of oral solid dosage form due to more flexibility and comfort. It is used as a novel approach, as it dissolve rapidly in mouth and directly reaches to the systemic circulation. FDOFs either dissolves or disintegrates within a minute, without needing water or chewing, enhances the potential for improved compliance in pediatrics and geriatric patients, who have difficulty in swallowing tablets or liquids. Thesefilms are used as practical alternative to traditional over the counter medicines, because of the various benefits of the film (fast, accurate dosing, safe, better efficacy, convenience and portability). Films are formulated using hydrophilic polymers, plasticizer, flavors, colors and sweeteners. This reviewdescribes about the formulation methodology, evaluation parameters and the future aspects of FDOFs.

Keywords: Fast dissolving oral films, Solvent casting technique, Hot melt extrusion, Rapid disintegration.

INTRODUCTION

Despite the tremendous advancement in the drug delivery system, oral route is the most preferred route of administration and tablet and capsules are the most preferred dosage form but now they experienced several limitations like chocking and swelling discomforts in the geriatric and pediatric patients. Among the plethora of avenues explored oral strips gain more attention as it emerging new platform for geriatric and pediatric patients[1].

Fast dissolving drug delivery system (FDDDS) was introduced in late 1970 as the alternative to conventional tablet, capsule and syrups especially for the geriatric and pediatric patients suffering from the dysphasia problem[2]. Fast dissolving tablets are the solid dosage form which disintegrates rapidly in the oral cavity without the need of water. Some problems are associated with the FDOFs like they are sometime difficult to carry, storing and handling (friability and fragility), these are prepared using the expensive lyophilisation method. To overcome these problems oral films were developed, which are very popular now a days [3].

The concept of oral film was come from confectionary industry. Oral films are the recent ultra-thin novel formulation of postage stamp size which contains active pharmaceutical ingredients and excipients [4]. Efficacy of API is improved as it dissolves in the oral cavity. Oral films disintegrate rapidly within seconds when it comes in contact with saliva without the need of water. Oral fast dissolving films are useful for the geriatric and pediatric patients and also for the patients suffering from emesis, diarrhoea, allergic attacks, cough, mental disorder, bedridden patients *etc*. Oral films are also used for local effects like local anesthetics for oral ulcers, toothaches, cold scars and teething[5]. Generally the shelf life of film is 2-3 years it depends on the API added to the film but films are very sensitive to environmental moisture.

In the oral cavity salivary gland, secretes saliva. Three salivary glands are present in the oral cavity i.e. parotid, submandibular and sublingual glands. Saliva is relatively less viscous as compared to GI fluids [6]. Saliva is mainly water which contains 1% organic and inorganic material. Saliva is a weak buffer and its pH ranges from 5.5-7. The total volume of saliva secreted from the salivary gland is 0.5-2 litres and it is the amount of saliva enough to hydrate oral mucosal dosage form [7].

The Potential Benefits [8], [9]

a) Large surface area promotes rapid disintegration and dissolution in the mouth cavity
b) Due to its flexible and less fragile nature, there is ease of transportation, storage and consumer handling
c) Ease of administration to patients who are mentally ill, disabled or non-cooperative
d) Precision in the administered dose.
e) Good mouth feel and offers water nil therapy
f) Rapid absorption, faster action and improved bioavailability

g) Improved patient compliance
h) Good stability and enhance the product life cycle

Major limitations of this dosage forms are, low dose loading capacity and limited taste masking options. Drawback of the film can be minimized by formulating an edible film which can adjust more dosage and bitterness of the drug can be masked by different taste masking processes. [10]

Biopharmaceutical Consideration

Before designing a new dosage form the biopharmaceutical factors need to be considered. Fast dissolving oral films quickly disintegrate, facilitating the absorption of drug from the mouth, pharynx and esophagus through the oral mucosa.[11] Factors like age, nature of the oral cavity, and blood flow to oral cavity should be considered. Distribution of drug depends on tissue permeability, perfusion rate; binding of drug to tissue, drug interaction *etc.* The duration and intensity of action depends on the rate of drug removal from the body or site of action.

There is no restriction to incorporate any therapeutic agent to this drug delivery system but the agents who have lower doses and need a quicker onset of the action are most preferable. The proportion of fast dissolving systems gets approved by different regulatory bodies for their therapeutic use. Several classes of drugs can be formulated as fast dissolving films including antiulcer, antiasthmatics, antitussives, expectorants, antihistaminics and NSAIDs. [12]

Ideal characteristics of drug candidate [13], [14]

a) The incorporating APIs should have a low dose of up to 40 mg
b) Drugs with low molecular weight are preferable
c) The drug should possess pleasant taste
d) The drug should have good solubility and stability both in water and saliva
e) It should be partially unionized at the pH of buccal cavity
f) It should have the ability to permeate oral mucosal tissue.

COMPOSITION OF THE SYSTEM

A typical composition of FDOFs formulation should contain the following excipients:

Drug 0-25 %

Water-soluble polymers	40 - 50%
Plasticizers	0 - 20 %
Fillers, color, flavors etc.	0-40 %

Different excipients are used to formulate the FDOFs

The formulation of fast disintegrating oral film involves the intricate application of aesthetic and performance characteristics like fast disintegrating, taste-masking, physical appearance, mouth feel etc. In the preparation of oral film, the selection of the film forming the polymer is very important and is the major non active ingredient. Important adjuvants include:

Film formers: These contribute a platform to the dosage form. Depending on the nature of the film former, physicochemical properties of the film can be modified. The obtained film should be tough enough so that there will not be any damage while handling or during transportation. The robustness of the film mainly depends on the type of polymer and the amount in the formulation. Mostly aqueous polymers are used as film formers. Some widely used film formers are hydroxyl propyl methyl cellulose (HPMC) of different grades, hydroxypropyl cellulose (HPC), polyvinyl alcohol (PVA), polyvinyl pyrrolidine (PVP), sodium alginate, sodium carboxy methyl cellulose (sodium CMC) and polyethylene glycol, and pullunan[15]

Stabilizing and thickening agents: The stabilizing and thickening agents are employed for the improvement of viscosity and consistency of dispersion or solution of the strip preparation. Natural gums as Xanthum gum, locust bean gum, carrageenan and cellulosic derivatives can be used in concentrations up to 5% w/w as stabilizing and thickening agents.

Plasticizers: Plasticizers impart strength, flexibility and gloss to the finished film product. The concentration of plasticizer should be optimized along with the film formers and other excipients to get a good, elegant film. Commonly preferred plasticizers are phthalate esters, phosphate esters, esters of oleate, adipate, sebacate, stearates, polyethylene glycol,triacetin, dimethyl phthalate *etc.*[16]

Surfactants: Surfactants are used to enhance the wettability of the film. Mostly nonionic surfactants are preferred like polyoxyethylene alkyl ethers (Brij), and polyoxyethylenesorbitan fatty acid esters (Tween).

Saliva stimulating agents: The purpose of using saliva stimulation agents is to increase the rate of production of saliva which aids in the faster disintegration of the rapid disintegrating strip formulations. They stimulate secretion of saliva, thus indirectly helping in the quick disintegration and dissolution of the film. Commonly used agents are citric acid, lactic acid, maleic acid, ascorbic acid*etc*.

Cooling agents: Cooling agents like monomethyl succinate, WS3, WS23 and Utracoll II can be added in the formulation for improvement of flavor strength and enhancement of the mouth feel of the product.

Solvent system: The solvent system may affect the surface texture and disintegration time of the film. Aqueous, organic, or a combination of both can be used as the solvent system.

Organoleptic agents: As the dosage form disintegrates in the mouth, it must have a pleasant taste and cooling sensation to the mouth. Organoleptics like sweeteners, flavors and colors are added so that the product can be better accepted. The most commonly used are mannitol, aspartame, sodium saccharin, thaumatin I and II, etc. The artificial sweeteners can be classified as 1st generation (saccharin, cyclamate, aspartame) or 2nd generation (acesulfame-K, sucralose, alitame,neotame).[17]

The flavors used should be compatible with the other ingredients. Vanilla, chocolate, coffee, orange, peppermint flavors are preferred. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Colors are selected to match with flavors for better acceptability. Water soluble dyes are commonly used.

TECHNOLOGIES INVOLVED IN FDOFS

1. XGel

XGel film manufacturing methods and technology, a great revolutionary product developed by BioProgress is offering a vibrant alternative available to the pharmaceutical industry. XGel film provides unique product benefits for healthcare and pharmaceuticals. It is a non-animal derived product, suitable for vegetarians and continuous production processing provides an economic and competitive manufacturing platform. XGel film can be taste masked, coloured, and layered, 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

different water-soluble polymers, specifically optimized for the intended use and generally regarded as safe (GRAS).[18]

2. Soluleaves

Soluleaves is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. This technology can be used to efficiently deliver both active ingredients such as OTC prescription drugs and nutraceuticals to the oral cavity, in a pleasant and easily portable form. On contact with saliva, the designed film dissolved rapidly and quickly releases the active ingredients and flavours. In view of pharmaceutical applications, this method of administration is especially useful for pediatric or geriatric patients who may have difficulty swallowing conventional tablets or capsules. This dosage form can be used for cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. Muco-adhesive soluleaves films can also be designed to adhere to mucous membrane and allow slow release of the active ingredient. [19]

3. Wafertab

Patented 'Wafertab' is a wafer, employed as a drug delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting. The system provides rapid dissolution and release of active pharmaceutical agents when the strip comes into contact with the saliva inside the buccal cavity. The wafertab film strip can be flavored for improved taste masking. Wafertab can be prepared in a variety of shapes and sizes and is an ideal method for the delivery of therapeutic agents, which desire fast release for patients who have swallowing difficulty. [19]

4. Foamburst

Foamburst, a special variant of the soluleaves, which got a new patent granted in 2004, is a capsule form made of foamed film. An inert gas is blown into the film during production, resulting in a film with a honeycombed structure. To produce specific taste-burst characteristics or deliver active drugs, the voids in the film may be gas filled. The designed light honeycombed structure results in capsules that dissolve rapidly, causing a melt in the mouth sensation. [18]

5. Micap

Micapplc signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the BioProgress water-soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4 bn global market for smoking cessation products (SCPs).[18]

TECHNOLOGIES FOR DEVELOPMENT OF FDOFs

A combination of different techniques such as rolling method solvent casting, solvent spraying, hot-melt extrusion, and solid dispersion extrusion are used for manufacturing fast disintegrating oral films. Among them, casting and spraying techniques are simple, reproducible and successful processes to develop the films.

1. Rolling method

In this method, a solution/suspension of drug with film forming polymer is prepared and subjected to the roller. The solution/suspension should have specific rheological consideration. The solvent is mainly water and a mixture of water and alcohol. [20] The film is dried on the rollers and cut as shown in Figure 1.

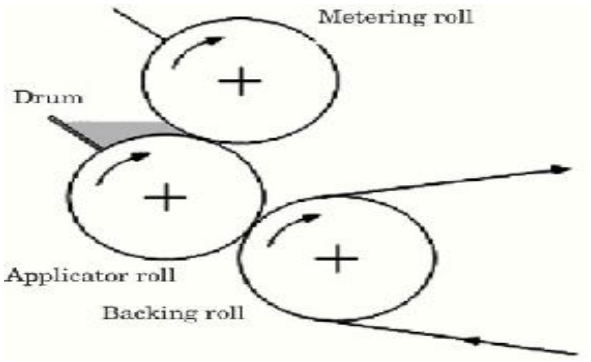

Fig. 1: Three roller coating film forming unit.

2. Solvent casting technique

In this process the film forming agents are soaked in a suitable solvent overnight. Other excipients along with the drug are added and mixed well in the solution. The liquid is poured over a suitable casting mould, generally a petridish, to get a film of desired thickness. [21] The selection of solvent essentially depends on the API to be incorporated into the film. The physiological properties of the API like shear sensitivity, heat sensitivity, the polymorphic form of the API employed, and compatibility of the API with solvent and film based

excipients are studied critically. The predominant factors to be considered are liquid rheology, desired mass to be casted and uniformity of the drug content. Solvent systems in the preparation of solution or suspension should be selected carefully and more preferably from ICH lists. The clearance or tolerance between the roller and the substrate determines the required thickness of the film. Heating processes can be used to assist the complete dissolution of materials. Mixing may cause the formation of air bubbles and their entrapment during the solution preparation. Air entrapment may tend to produce non uniform films. [22]Deaeration step is imperative to get a uniform film which is achieved by vacuum assisted machines as shown in Figure 2.

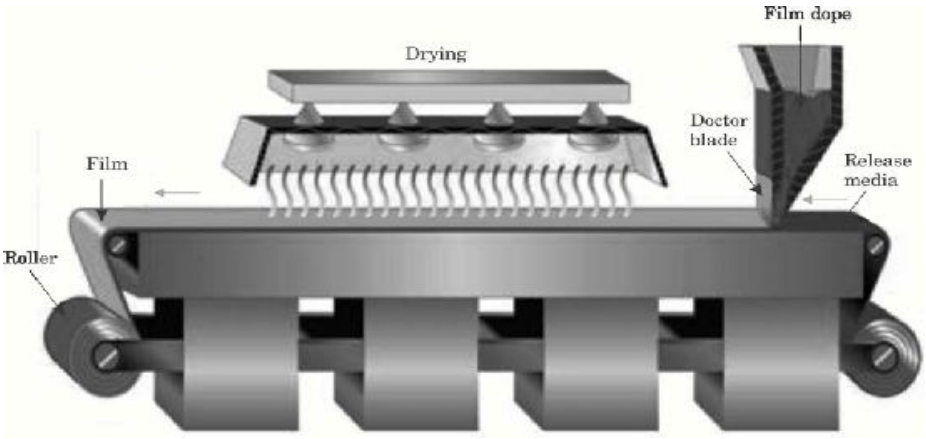

Fig. 2: Solvent casting technique.

Another important aspect, *i.e.* moisture contents in the solution, can cause changes in the mechanical properties of the films such as flexibility, tensile strength, folding endurance, Young's modulus, elongation, *etc.* [22] formulated levocetirizine hydrochloride oral film with pullulan polymer using solvent casting method. The optimized films of levocetirizinedihydrochloride were obtained which satisfied all the requirements of an ideal fast dssolving oral film.

3. Semi solid casting

In the semisolid preparation water soluble polymers are added and to this preparation, acid insoluble polymer (*e.g.* cellulose acetate phthalate, cellulose acetate butyrate) which is prepared by ammonium and sodium hydroxide, and then the surplus amount of plasticizer form a gel which is casted. [22]

4. Hot melt extrusion

Hot melt extrusion is commonly used to prepare granules, sustained release tablets, and transdermal and transmucosal drug delivery systems. This technique involves shaping a polymer into a film via the heating process rather than through the conventional solvent casting method. In this method, API and other ingredients are mixed in a dry state, then subjected to the heating process and then extruded out inmolten state. These processes are without involvement of any solvent systems. The molten mass thus formed is used to cast the film. The films are further cooled and cut to desired size. This process is not suitable for the thermolabile APIs, due to the use of very high temperature. Optimization of speed of casting and drying time are important from the commercial scale output. This process includes lower temperature and shorter residence times of the drug carrier mix, absences of organic solvents, minimum product wastage, good control of operating parameters and possibilities to scale up. [23]Successfully formulated piroxicam film with Maltodextrin plasticized by glycerin employing this method.

5. Solid dispersion extrusion

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.

6. Spray drying technique

A solvent system containing film former and other excipients are sprayed or coated on suitable carrier material, dried and peeled off to get the film. The carrier materials used for film are glass, non-siliconizedkraft paper or polyethylene film *etc.* [23]

PHYSICOCHEMICAL EVALUATION

1. Physical appearance

Film was visually inspected for color, clarity, flexibility and smoothness by feel or touch.

2. Weight uniformity and Thickness

The assessment of weight and film thickness was done in 10 different randomly selected films from each batch. Films were directly weighed on a digital balance and film thickness was measured using a screw gauge.

3. Drug Content Uniformity

Drug content uniformity was determined by dissolving the 4cm^2 film in 100 ml of phosphate buffer (pH 6.8) for 8 h by homogenization under occasional shaking. Then 5 ml solution was taken and diluted with phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45 µmWhatmanfilter paper. The drug content was then determined after proper dilution at spectrophotometer.[24]

4. Folding Endurance

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the films for five times. [24]

5. Surface pH

Films were left to swell for 1 hr on the surface of the agar plate,prepared by dissolving 2% w/v agar in warmed phosphate buffer solution, pH 6.8 under stirring and then poured the solution into the petridish till gelling/solidify atroom temperature. The surface pH was measured by means of pH paper placed on thesurface of the swollen film. The mean of three readings were recorded. [25]

6. Hydration study (water uptake/ swelling study)

Films (n=3) were weighed individually (W1) and placed separately in petri dishes containing 5 mL of phosphate buffer (pH 6.8) solution. The dishes were stored at room temperature. Then, films were removed and excess surface water was removed carefully using the filter paper after specified time intervals.[26] The swollen films were then again weighed (W2) and swelling index (SI) was calculated using the following formula.

$$\text{Swelling Index (SI)} = \frac{Wt - Wo}{Wo}$$

Where,W_t is the weight of the film at time "t" and W_o= weight of the film at t = 0.

7. Percentage moisture loss

The percentage moisture loss was determined by keeping the films in a desiccators containing anhydrous calcium chloride. After three days, the films were taken out and re-weighed; the

percentage moisture loss was calculated using formula:[27]

$$\% \text{ Moisture Loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} X\ 100$$

8. Tensile Strength

A small film strip was cut on a glass plate with a sharp blade. One end of film was fixed between adhesive tape to give support to film when placed in the film holder. Another end of film was fixed between the adhesive tape with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hooked was inserted. A thread was tied to this hook, passed over the pulley and a small pan attached to the end to hold the weights. A small pointer was attached to the thread, which travels over the scale affixed on the base plate. To determine tensile strength the film was pulled by means of pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The elongation was recorded as the distance travelled by the pointer before break of the film on the scale. The weight required to break the film was noted as break force. Tensile strength was calculated as:[28]

$$\text{Tensile strength} = \frac{\text{Break force}}{a.b}\left(1 + \frac{\Delta L}{L}\right)$$

Where a, b and L were width, thickness and length of film, and ΔL is the elongation at break.

***9. In vitro* release studies**

The release of drug from the prepared fast dissolving films of 4cm^2 calculated in phosphate buffer pH 6.8 at 37 ± 0.5º C.Each film was adhered to the side wall of a vessel (100 ml beaker) using cyanoacrylate adhesive. Adequate sink conditions were provided by placing 50 ml of phosphate buffer pH 6.8 in each vessel. Each covered vessel was fitted with a magnetic stirrer rotating at a rate of approximately 150 rpm. After time intervals each of 20, 40, 60, 80, 100 and 120 sec. 3 ml sample was withdrawn, filtered through a whattman filter paper and assayed spectrophotometrically. Immediately after each sample withdrawal, a similar volume of phosphate buffer pH 6.8 was added to the release medium to maintain the volume in the vessel constant. [29]

10. In vitro release kinetics

To establish a relationship between the release kinetics of the dissolution study, data obtained from *in vitro* dissolution study was fitted into various kinetic models: zero order as

cumulative percent of drug dissolved*vs.* time, first order as log cumulative percentage of drug remaining *vs.* time and Higuchi's model as cumulative percent drug dissolved*vs.* square root of time. To determine the mechanism of drug release, the data were fitted into Korsmeyer and Peppas equation as log cumulative percentage of drug released *vs.* log time, and the exponent n was calculated from slope of the straight line. For slab matrix, if exponent is 0.5, then diffusion mechanism is fickian; if 0.5<n <1.0, mechanism is non- fickian,n = 1 to Case II (relaxational) transport, and n > 1 to super case II transport.[30]

11.Stability studies

The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The formulations F2 and T8 were subjected to stability studies for 3 months using storage conditions 45 °C / 75% RH as per ICH guidelines. Throughout the course of aging study, triplicate samples were taken at three sampling times (*i.e.* 0, 1 month and 3 month) and evaluated for physical texture and drug content.[29]

PACKAGING

A variety of packaging options are available for fast dissolving films. In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used. Applied Pharma Research (Switzerland)-Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the mouth dissolving films. The Rapid Card is exactly the same size as a credit card and holds three mouth dissolving films on each side. Every dose can be taken out individually, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet and have it readily available.[31]The material selected must have the following characteristics:

- They must protect the preparation from environment conditions.
- They must be non-toxic, non-reactive with the product and FDA approved.
- They must not impart to product tasted or odors.
- They must meet applicable tamper-resistant requirement

Foil, paper or plastic pouches: The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistance, but also by the proper selection of

material,a package with a high degree of environmental protection is needed. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.[32]

Single pouch and aluminum pouch: Soluble film drug delivery pouch is a peel able pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a two structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

Blister card with multiple units: It consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The cavity form material is a plastic, which is designed to protect the dosage form from moisture.

Barrier films: Theseare used where drug preparations are extremely sensitive to moisture. Several materials may be used to provide moisture protection such as polychlorotrifluoroethylene (PCTFE) film, polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapor barrier. [32]

CONCLUSION

Meanwhile, many pharmaceutical industries delivers medicinal or over the counter products using this technology. Fast dissolving films have gained popularity as dosage forms for the mouth freshners. The FDOFs are seemed to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Films have several advantages over the conventional dosage forms. So, they are of great importance during the emergency cases such as allergic reactions and asthamatics attacks whenever immediate onset of action is desired. This review is an effort to combine the knowledge available on fast dissolving oral films.

Table 1: Examples of commercially available FDOFs.

PRODUCT	ACTIVE DRUG	DOSE (mg)	APPLICATION	COMPANY
Klonopin wafers[11]	Clonazepam	0.12 - 2	Treatment of anxiety	Solvay Pharmaceuticals
Triaminic[6]	Dextromethorphan HBr	5 - 7.5	Seasonal allergy	Novartis
Triaminic[6]	Diphenhydramine HCl	12.5	ThinStrip for Long acting cough	Novartis
Theraflu[3]	Dextromethorphan HBr	10 - 20	For Long acting cough	Novartis
Gas-X[3]	Simethicone	62.5	Gas-X ThinStrip Anti Gas	Novartis
Sudafed PE [19]	Phenylephrine HCl	10	Decongestant oral strips	Pfizer
Benadryl[3]	Diphenhydramine HCl	12.5	Antihistaminic oral strips	Pfizer
Chloraseptic[13]	Benzocaine: Menthol	3 - 3	Chloraseptic Relief Strips	Prestige
Suppress[19]	Dextromethorphan	2.5	Suppress Cough Strips	InnoZen
Suppress[19]	Menthol	2.5	Suppress Herbal Cough relief Strips	InnoZen
Orazel[6]	Menthol/Pectin	2 - 30	Cough and cold relief strips	Del
Listerine[3]	Cool mint	-	Antiseptic mouthwash	Pfizer
Little Colds [3]	Pectin	-	Sore throat strips	Prestige brands
Eclipse [19]	Sugarfree mints	-	Chewing gum, Breath mint	Wringley's
Donepzil[11]	Donepzil HCL	5 - 10	In *Alzheimer's disease*	Labtec GmbH
Ondansetron[11]	Ondensteron	4 - 8	Antiemetic, helps in nausea and vomiting	Labtec GmbH

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