Original Article

Polymers Use In Mouth Dissolving Formulation: A Review Article

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Abstract

Technology advancements in recent years have made effective dose alternatives to the oral route for patients who are young,old, immobile, queasy, or unable to comply. Fast-dissolving oral thin film is a solid dosage form, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing. Oral fillm includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, film stabilizing agents, sweeteners, flavours, colors, saliva stimulating agents, preservatives, surfactants etc but the first and far most a very essential ingredient which helps in film formation is a Polymer. Fast dissolving 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. For quickly disintegrating films, wafter-soluble polymers are utilised as film formers.T watersoluble polymers give the films quick disintegration, a pleasant mouthfeel, and mechanical qualities.

Keywords: Plasticizers, Fast dissolving mouth film, fast dissolving thin film, oral mouth film.

INTRODUCTION

The mouth dissolving film (MDF) can be used for delivering a drug systemically to achieve the therapeutic or pharmacological effect. MDF formulations avoid the first pass effect, their systemic bioavailability has increased [1,2]. The oral cavity is a selective site for drugs that are to be administered systemically. This might be because the film has a high surface area that makes it easier to absorb nutrients, reduce discomfort, and swallow the film without water [3]. Technology advancements have provided alternatives to oral dosing forms.

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 have been embraced by pharmaceutical companies and consumers alike as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs provide fast, accurate dosing in a safe, efficient, portable format that does not require water or measuring devices. OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in seconds, allowing one or more APIs to be released quickly. [3] When placed in the mouth without drinking water or chewing, fast-dissolving oral thin film disintegrates or dissolves within 1 minute. After disintegrating in the mouth, the drug's clinical effect was enhanced by pre-gastric absorption from the mouth, pharynx, and oesophagus as saliva passed down into the stomach. In such cases, drug bioavailability is significantly higher than that observed with conventional tablet dosage form. In terms of flexibility and comfort, fast dissolving films may be preferred over adhesive tablets. [4] Furthermore, they can avoid the relatively short residence time of oral gels on the mucosa. Oral thin film has main four types: Flash release film, flash dispersible film, Nondisintegrating mucoadhesive film,medium disintegrating mucoadhesive film.[5]A good film should be flexible, elastic, and soft, but also strong enough to withstand breakage caused by stress from mouth movements. In order to be retained in the mouth for the desired duration of action, it must also have good bioadhesive strength. [6]Oral films are made of a variety of ingredients, including polymers, active pharmaceutical ingredients, film stabilising agents, sweeteners, flavours, colours, saliva-stimulating agents, preservatives, and surfactants. However, the first and by far the most important component that aids in film formation is a polymer. Hydrophilic polymers are used to create a film that quickly dissolves on the tongue or in the buccal cavity, allowing the medicine to be absorbed into the bloodstream when in contact with liquid [3].Hydrophilic polymers are used to create a film that quickly dissolves on the tongue or in the buccal cavity, allowing the medicine to be absorbed into the bloodstream when in contact with liquid [3].

IDEAL PROPERTIES OF MOUTH DISSOLVING POLYMERS

The ideal characteristics of MDFs are as follows [8-10]:

- It should be thin, flexible, and easy to handle.
- The films should be transportable, not sticky and keep a plane form without rolling up.
- It should have good wetting and spreadability property.
- It should have a good mouth feel property.
- The polymers employed should have good shelf life.

- It should be easy to administer.
- The film should offer agreeable taste and a satisfying mouth-feel.
- The disintegration time should be as rapid as possible.
- Film surface should be smooth and uniform.
- It should remain physically and chemically stable during its shelf life.
- It should be cost effective and ease of commercial production.
- It should have low sensitivity to environmental/atmospheric conditions such as humidity and temperature.
- Size of a unit film should not be too bulky that it will affect the patient's compliance.

ADVANTAGE OF MOUTH DISSOLVING FILM (MDF'S)

Mdf's advantages are as follows (8-11)

- It can be taken without water.
- It disintegrate/dissolve quickly in mouth.
- Flexible and light in weight.
- It is appropriate to all age group.
- Appropriate for patients who are ill or uncooperative.
- Films remain stable for longer time as it is a solid dosage form until its administration
- The drug absorbed directly from film formulation into the blood, so it avoids undergoing first-pass hepatic metabolism which seen in conventional dosage forms.

DISADVANTAGES OF MDF'S

Mdf's disadvantage are as follows (7-11)

- Drug(s) which requires to take in high doses cannot be incorporated into films.
- Maintaining dosage uniformity is challenging task for the films.
- Moisture sensitivity.
- Require special packaging.
- API's which are unstable at pH of the saliva cannot be designed in the form of film.
- API's which can cause irritation of the oral mucosa cannot be administered.

Various polymers are used for preparation of fast dissolving oral films. Some of them are discussed below together with their physichochemical properties and film forming abilities.

CLASSIFICATION OF POLYMERS USE IN MOUTH DISSOLVING

There are three main types of polymers use in mouth dissolving formulation.
It is based on it's biodegradablility.
The types of polymers are as follows :

1. Natural polymers
2. Synthetic polymers
3. Semi-synthetic polymers

NATURAL POLYMERS

Natural polymers which are used in mouth dissolving formulation are listed below in the table.

Sr. No	Natural polymer	Market drug	Disintegration time
1	Mango peel pectin	Aceclofenac	11.59 s
2	Dehydrated banana powder	Ondasetron hcl	15-36 s
3	Gellangum	Metronidazole	155 s
4	Gum karaya	Amlodipine, granisetron hydrochloride	17.10 s
5	Sodium alginate	Medicinal carbon[manitol]	3-8 s
6	Gelatin	Montelukast sodium	17 s

1. Mango peel pectin :

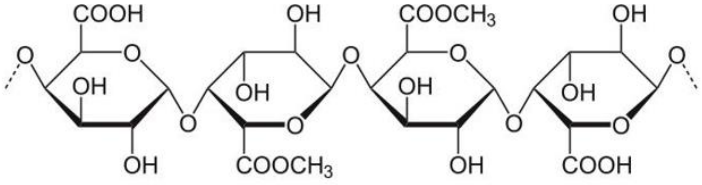

Figure 1: STRUCTURE OF MANGO PEEL PECTIN

Mango peel, which accounts for 20- 25% of mango processing waste, was noticed to be a good source for the extraction of high-quality pectin, as well as the preparation of film and acceptable jelly. Pectin is an in volute heteropolysaccharide which is a hydrophilic colloid. Malviya et al. (2011) investigated and discovered that while mango peel pectin is not as

strong as synthetic. Superdisintegrants, it may be used in the formulation of fast dispersible tablets due to its good solubility and higher swelling index [17, 18]. Extracted pectin was soluble in warm water while insoluble in organic solvents. Results of evaluated parameters showed that mango peel derived pectin can be used as pharmaceutical excipient to prepare solid oral dosage form.

2. DEHYDRATED BANANA POWDER (DBP)

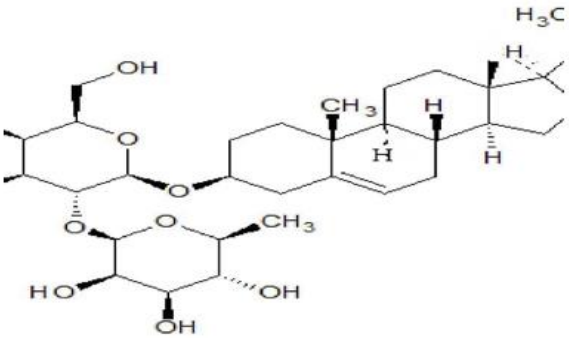

Figure 2: STRUCTURE OF DBP

Plantain is another name for banana dehydrated bananaow pBP) is derived from the banana varieties ethan and nenthran (nenthra vazha) and belongs to the Musaceaeam. It contains vitamin A, so it is utilized in the treatment of gastric ulcer and diarrhea.It also contains vitamin B6, which helps to reduce stress and anxiety. Because of its high carbohydrate content, it is a very good source of energy, and it contains potassium, which is responsible for more predominant brain functioning [26].

3. GELLAN GUM

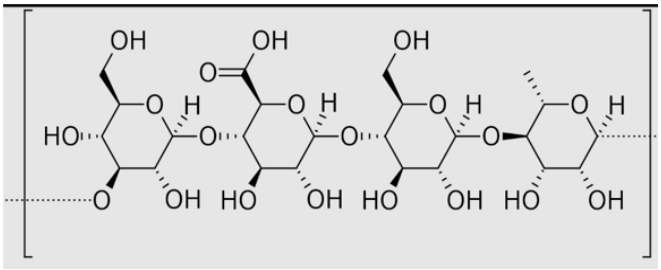

Figure 3: STRUCTURE OF GELLAN GUM

Gellan gum is a natural polysaccharide derived from the bacteria and has potential applications in this area owing to its biocompatibility and flexibility for modification. The gellan gum repeating unit is a tetrasaccharide composed of l-rhamnose, d-glucuronic acid, and two d-glucose residues. Lysozyme secreted by monocytes and neutrophils (2), like other polysaccharides, can degrade the backbone. (3) Degradation kinetics can be controlled by varying the degree of crosslinking as well as the type of crosslinking bond, which can be accomplished by varying thephysical or chemical linkages. (4) As with changing degradation profiles, changing the type and degree of cross-links can alter mechanical properties. By charge-shielding the polymer chains and promoting physical cross-links and aggregation, cations can be used to cross-link gellan gum gels. Multivalent cations, in particular, act as bridges between carboxyl groups, reducing electrical repulsion. (5) While monovalent cations can screen the charges on gellan molecules, the interaction is much weaker than the ionic bonds formed by carboxylic acids and divalent cations. (5) As a result, physically cross-linked gellan gum hydrogels will lose their physiological stability as divalent cations are replaced by monovalent cations at much higher concentrations in vivo. (4)

4. GUM KARAYA

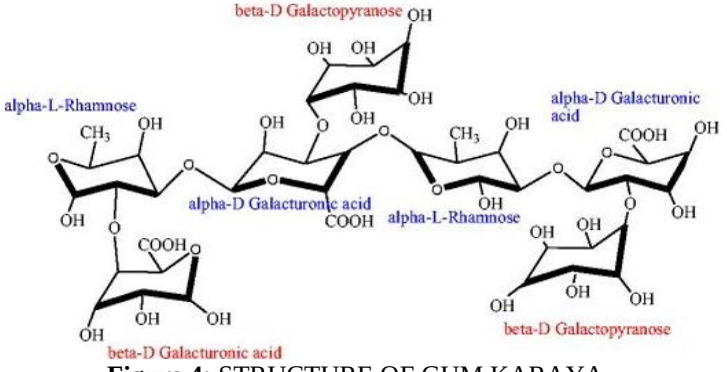

Figure 4: STRUCTURE OF GUM KARAYA

Gum karaya or gum sterculia, also known as Indian gum tragacanth, is a vegetable gum produced as an exudate by trees of the genus Sterculia. Gum karaya is an acid polysaccharide composed of galactose, rhamnose, and galacturonic acid. It's used in foods as a thickener and emulsifier, as a laxative, and as a denture adhesive. Due to their similar physical characteristics, it is also used to adulterate Gum tragacanth. Gum karaya can be obtained from the tree Sterculia urens. Gum karaya can be utilized as an alternative superdisintegrant to commonly available synthetic and semisynthetic superdisintegrants due to its low cost, biocompatibility as well as facile availability [11] Gum karaya is a heavily acetylated polysaccharide composed of chains of α-d-galacturonic acid and α-l-rhamnose. The acid groups are glycosylated with β-d-galactose or β-d-glucuronic acid residues, whereas about half of the rhamnose groups carry β-d-galactose units as side chains. (Figure 4)

5. SODIUM ALGINATE

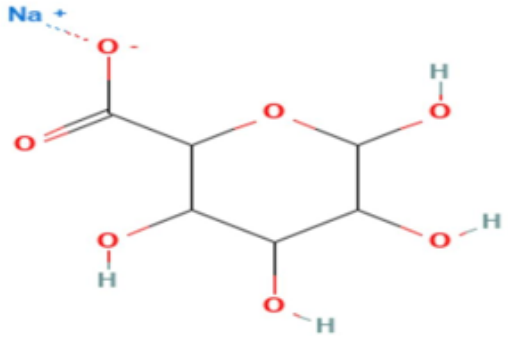

Figure 5: STRUCTURE OF SODIUM ALGINATE

Sodium alginate is natural polymer, sodium alginate is primarily composed of the sodium salt of alginic acid, which is a polyuronic acid mixture composed of D-mannuronic acid and L-guluronic acid residues. Alginate is an indigestible biomaterial produced by brown seaweeds (Phaeophyceae, mainly Laminaria). It can be found in brown algae cell walls as the calcium, magnesium, and sodium salts of alginic acid. Because of its unique colloidal properties, such as thickening, stabilising, suspending, film forming, gel producing, and emulsion stabilising, alginate has the potential to form a biopolymer film or coating component [23]. Because of their hydrophilic nature, edible films made from alginate are strong but have poor water resistance. When compared to synthetic films, the water permeability and mechanical properties are considered moderate. Starch can improve the mechanical properties of an alginate film [24]. Used as film base material. The addition of sorbitol or manitol in it caused improvement in adsorption ability of medicinal carbon film as compared to its powder form along with sufficient strength and disintegration time. [34]

6. GELATIN

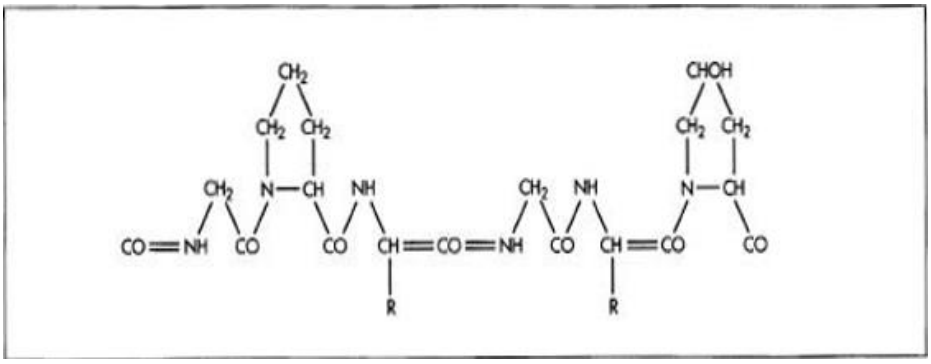

Figure 6 : STRUCTURE OF GELATIN

Gelatin is made by thermally denaturing collagen, which is isolated from animal skin, bones, and fish skins. Gelatin is a generic term for a mixture of purified protein fractions obtained from either partial acid hydrolysis (type A gelatin) or partial alkaline hydrolysis (type B gelatin) of animal collagen, or a combination of the two.[31]At temperatures above 40°C, it dissolves readily in water, forming a viscous solution of random-coiled linear polypeptide chains. Gelatin is a generic term for a mixture of purified protein fractions obtained from either partial acid hydrolysis (type A gelatin) or partial alkaline hydrolysis (type B gelatin) of animal collagen, or a combination of the two. The protein fractions are almost entirely made up of amino acids connected by amide linkages to form linear polymers. Until the 1960s, the use of mammalian gelatin in the production of edible films or coatings was extensively researched, resulting in numerous patents, primarily in the pharmaceutical field [27]. However, in the year 2000, gelatin films made primarily of fish gelatin were brought back to the attention of researchers. Gelatin films were discovered to dissolve quickly, be excellent flavour carriers, and have a smooth mouth feel [27].

SYNTHETIC POLYMERS

Synthetic polymers which are used in mouth dissolving formulation are listed below in the table.

Sr no	Synthetic polymers	Market drug
1	Polyethylene oxide	Ondansetron HCl
2	Polyvinyl alcohol	Levocetrizine dihydrochloride
3	Polyvinyl pyrrolidone (PVP)	Indomethacin
4	Hydroxy propyl cellulose	Lidocaine
5	Hydroxypropyl methyl cellulose	Verapamil dexamethasone

SYNTHETIC POLYMERS

1. POLYETHYLENE OXIDE

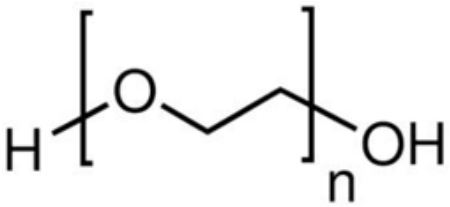

Figure 7: STRUCTURE OF POLYETHYLENE OXIDE

Polyethylene oxide (PEO) or POLYOX is a synthetic polyether or water soluble resins that is readily available in a wide range of molecular weights. PEGs are materials with a molecular weight of 100,000, whereas Poly ethylene oxides are higher molecular weight polymers. Poly ethylene oxides are white, free-flowing hydrophilic crystalline powders with an average particle size of around 150 μm. It is a biocompatible polymer [46]. PEO has a relatively high melting point, good structural integrity, a low glass transition temperature, low toxicity, and biocompatibility. It is a non-ionic, water-soluble resin that is highly hydrophilic and has excellent lubricating, binding, and film-forming properties.

2. POLYVINYL ALCOHOL

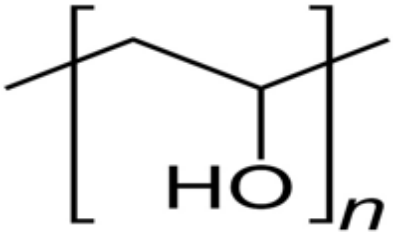

Figure 8: STRUCTURE OF POLYVINYL ALCOHOL

Polyvinyl alcohol (PVOH, PVA) is a synthetic polymer that is water soluble and has excellent film forming, emulsifying, and adhesive properties. It is also oil, grease, and solvent resistant. It has no odour and is nontoxic. It has high tensile strength and flexibility, as well as high oxygen and aroma barrier properties. The water, which acts as a plasticizer, reduces the tensile strength while increasing the elongation and tear strength. PVA is completely biodegradable and dissolves quickly. The melting points of Pva are 230°C and 180-190°C (356-374 degrees Fahrenheit) for fully and partially hydrolyzed grades, respectively. [43]The solvent casting method was used to create an oral film using a blend of HPMC and PVA, either alone or in combination. Rapid dissolution.

3. POLYVINYL PYRROLIDONE (PVP)

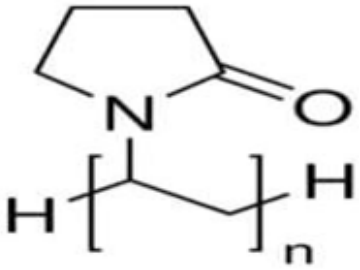

Figure 9: STRUCTURE OF POLYVINYL PYRROLIDONE

PVP, also known as **Polyvidone** or povidone, is a water-soluble polymer derived from the monomer N-vinyl pyrrolidone [48]. It is biocompatible, non-toxic, essentially chemically inert, temperature resistant, pH-stable, non-ionic, and colourless. Because polyvinyl pyrrolidone films are brittle, co-povidone is mixed with polyvinyl pyrrolidone to make flexible fast disintegrating strips [49]. Three grades of PVP K 10, 25, 40 were used. Indomethacin was seen to crystallize

from all PVP grades over 24-48 hrs at two study temperatures 25 and 37 ºC.

4. HYDROXYPROPYL CELLULOSE

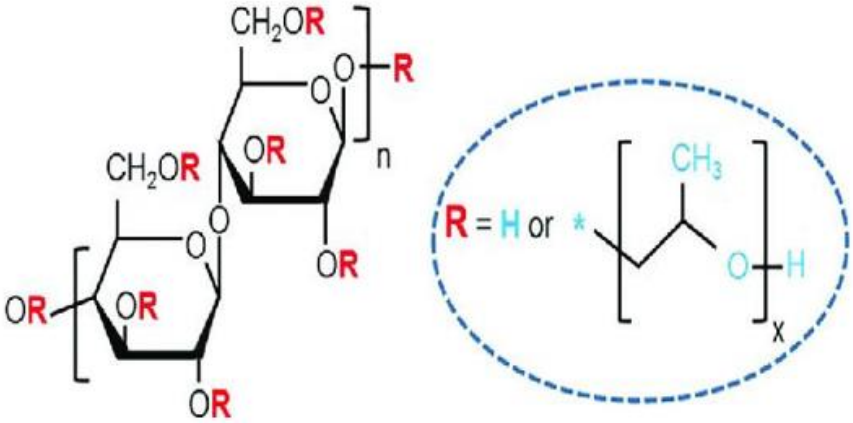

Figure 10: STRUCTURE OF HYDROXYPROPYL CELLULOSE

Cellulose as partially substituted poly (hydroxypropyl) ether of cellulose.The thermoplastic polymer hydroxypropyl cellulose (HPC) is non-ionic and water soluble.HPC creates extremely flexible films and has great surface characteristics. Stiff films are produced using polymers with very high glass transition temperatures.The produced films were found to be stiff, with a high elastic modulus and a very low percent elongation (less than 5%), and to display brittle fracture due to HPC's relatively high glass transition temperatures (compared to other film forming polymers).The films have a strong carrying capacity and reasonable clarity, and they often dissolve slowly. HPC has a strong ability to create films. It can be employed alone or in conjunction with hypromellose to make flexible films since it gives its solution low surface and interfacial tension. [39, 40]

5. HYDROXYPROPYL METHYL CELLULOSE

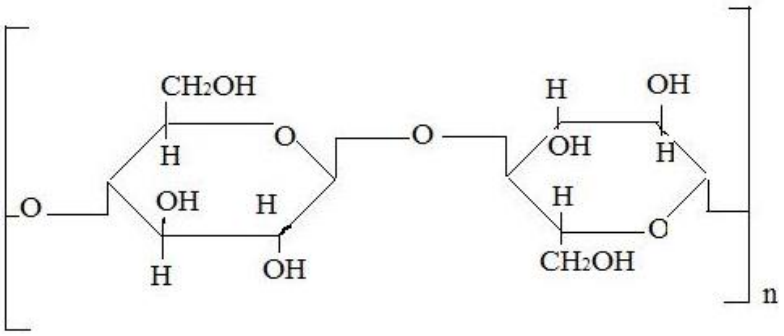

Figure 11: STRUCTURE OF HYDROXYPROPYL METHYL CELLULOSE

Hydroxypropyl Methyl Cellulose (HPMC) or hypromellose is a partly O- methylated and O-(2 Hydroxypropylated) cellulose. It is well-known for its excellent acceptability and good film forming properties. Aqueous solutions are used to create HPMC films that are transparent, tough, and flexible. HPMC polymer has a high glass transition temperature and is classified based on substituent content and viscosity, which influences the solubility-temperature relationship. Because of their low viscosity, lower grades of HPMC, such as Methocel E3, E5, and E15, are particularly useful for film formation. HPMC films are effective moisture and oxygen barriers. HPMC is also used for aqueous coating, but it has low water solubility and the resulting film has poor adhesion and mechanical strength.[39]

Table: - Current status of fast dissolving oral films

Drug	Polymer	Plasticizer	Ref. No.
Ambroxol hydrochloride	HPMC	PEG 4000	45
Amlodipine besylate	Sodium algenate	Glycerine	46
Aripiprazole	HPMC, Maltodextrin	PEG-1000	47
Sertraline	PVA	PEG-400, PG	48
Dexamethasone	HPMC, HPC, MCC		49
Dicyclomine	HPMC, PVA	PEG-400	50
Famotidine	HPMC K15M,	PEG600	51
Piroxicam	Maltodextrin	Glycerol	52
Fentanyl	Polyvinylpyrrolidone	Triethylcitrate	53
Ketorolac	HPMC E15, Na-CMC	PG	54
Levocetrizine	Sodium algenate	Glycerine	55

Hydrochloride			
Cetrizine Hydrochloride	Pullulan PI-20	PEG 400)	56
Metoclopramide	HPMC E6, Na- CMC	GLYCEROL	57
Montelukast sodium	Gelatin, MCC, PVP	PEG 400	58
Ondensetron hcl	HPMC	PEG 400	59,60
Rizatriptan	PVP, Na- CMC	Mannitol	61
Zolmitriptan	HPMC	PG	62

CONCLUSION

By altering the rate at which the films dissolve, the release of the drug can be either rapid or gradual. The consumer healthcare branch of Pfizer's Warner-Lambert company developed the breath refreshing strip and introduced Listerine Pocket PaksTM in 2001. In September 2003, Prestige Brands International released Chloraseptic Relief Strips in the United States to treat sore throats. These were the first oral thin film product to contain a drug. This innovative delivery method, which is a medicated oral strip built as a proprietary bilayer system, was created by Zengen Inc. These films typically include an effective amount of the active ingredient, water-soluble hydrocolloids including HPMC, pullulan, pectin, and carboxymethyl cellulose, as well as other additives like flavourings, plasticizers, and preservatives.The thickness and hydrocolloid combination of thin films affect how they dissolve and disintegrate. MDFs naturally dissolve in water and break down in the mouth. The dosage may stick to any mucosal surface in the oral cavity due to its muco-adhesion capabilities till full breakdown. After total disintegration, the API may be absorbed through the buccal mucosa. Swallowing saliva containing the dissolved API may also result in esophageal absorption. In the end, the majority of the dose is absorbed in the GI tract similarly to how a regular tablet would be. Traditional oral dose forms need a predetermined period of time for stomach juices to completely breakdown the tablet or capsule

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