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A REVIEW ON NATURAL POLYMER USED FOR RAPID ORAL THIN FILM FORMULATION

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ABSTRACT

Current developments in the technology have presented viable dosage alternatives from oral route for paediatrics, geriatric, bedridden, nauseous or noncompliant patients. Oral thin film, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. 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 film 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. Water-soluble polymers are used as film formers for fast dissolving films. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. Fast-dissolving oral thin film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices. In this review article the different polymers used for preparation of fast dissolving oral thin film like Pullulan, Gelatin, Sodium Alginate, Pectin, Rosin, Starch, Chitosan are discussed together with their physicochemical properties and film forming properties.

INTRODUCTION

The oral mucosal epithelium is a 40-50 cell layer called mucus that is made up of carbohydrates and proteins. The mucosal thickness at the mouth base, tongue, and gums ranges from 100 to 200 µm.[1] The submucosal layer releases a small amount of gel-like fluid known as mucus, consisting of 90%-99% water, 1%-5% water-insoluble glycoprotein, and components such as proteins, enzymes, electrolytes, and nucleic acids.On the other hand, the salivary glands consist of lobules that secrete saliva and parotid from the salivary duct near the sublingual canals and submandibular teeth. Small salivary glands are most often found on the lips and cheek mucosa. The total amount of saliva secreted in 1 min is approximately 1-2 mL. Saliva is composed of mucus, water, amylase (enzyme), lysozyme, mineral salts, immunoglobulins, and blood clotting factors. Mucin and saliva also serve as a barrier for the oral mucosa.[1,2]The mucosal epithelial

structure contains two different areas, the membrane of the stratified epithelium, which is a lipophilic area and space between cells, and a more hydrophilic area.[3] The oral mucosa has a capability between the intestinal mucosa and the epidermis in terms of permeability to substances. It is estimated that the permeability of the buccal mucosa is 4-4000 times better than that of the skin.[2] The mucosal epithelium offers two main drug absorption pathways, the paracellular pathway (intercellular) and the transcellular pathway (intercellular). The lipophilic structure of the cell membranes facilitates the passage of molecules with a high partition coefficient through the cells, while the polar nature of the intercellular space facilitates the penetration of more hydrophilic molecules. The hydrophobic, hydrophilic, or amphiphilic nature of the drug molecule determines its absorption.[2,3] Many pharmaceutical preparations are applied in tablet, granule, powder, and liquid form. In general, a tablet design is in a form presented to patients to swallow or chew a precise dose of medication. However, especially geriatric and paediatric patients have difficulty chewing or swallowing solid dosage forms.[4] Therefore, many children and elderly people are reluctant to take these solid dosage forms owing to fear of asphyxiation. Orally dissolving tablets (ODTs) have emerged to meet this need. However, for some patient populations, the fear of swallowing the solid dosage form (tablet, capsule), and the risk of asphyxiation remains despite short dissolution/disintegration times. Oral thin film (OTF) drug delivery systems are a preferable alternative under these conditions. The oral bioavailability of many drugs is insufficient due to the enzymes, common firstpass metabolism, and pH of the stomach. Such conventional drugs have been administered parenterally and have shown low patient compliance. Situations like these have paved way for the pharmaceutical industry to develop alternative systems for the transportation of drugs by developing thin dispersible/ dissolving films in the mouth.[1,5,6] Fear of drowning, which may be a risk with ODTs, has been associated with these patient groups. Rapid dissolution/disintegration of OTF drug delivery systems is a preferable alternative to ODTs in patients with fear of asphyxiation. When they are placed on the tongue, OTFs are immediately wetted with saliva. As a result, they are dispersed and/or dissolved to release the drug for systemic and/or local absorption. ODTs are fragile and can break during transport. Therefore, oral fast disintegrating/dissolving OTF drug delivery systems are developed as an alternative.[7] Oral disintegrating/dissolving films or strips can be defined as follows: "These are drug delivery systems that they are quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue".[8] The sublingual mucosa has high membrane permeability due to its thin membrane structure and high vascularisation. Due to this rapid blood supply, it offers very good bioavailability.[4,9] Enhanced systemic bioavailability is owing to skipping the firstpass effect and better permeability is owing to high blood flow and lymphatic circulation. In addition, the oral mucosa is a very effective and selective route of systemic drug delivery because of the large surface area and ease of application for absorption.6 In general; OTFs are characterized as a thin and flexible polymer layer, with or without plasticizers in their content. They can be said to be less disturbing and more acceptable to patients, as they are thin and flexible in their natural structure. Thin films are polymeric systems that provide many of the requirements expected of a drug delivery system. In studies, thin films have shown their abilities such as improving the initial effect of the drug and duration of this effect, decreasing the frequency of dosing, and increasing the effectiveness of the drug. With thin-film technology, it can be beneficial to eliminate the side effects of drugs and reduce common metabolism procured by proteolytic enzymes. Ideal thin films should possess the desired properties of a drug delivery system, such as a suitable drug loading capacity, rapid dispersion/dissolution, or prolonged application and reasonable formulation stability. Also, they must be nontoxic, biodegradable and biocompatible.[10]

Oral fast-dissolving film is generally another dose structure in which thin film is readied utilizing hydrophilic polymers, which quickly disintegrates on the tongue or buccal cavity.[10] As the strip framing polymer (which shapes the stage for the FDF) is the most basic and significant part of the FDF at any rate 45%w/w of polymer ought to, for the most part, be available dependent on a complete load of the dry film however regularly 60 to 65%w/w of polymer is wanted to get wanted properties.[11] The polymers employed in the oral film preparation should be-- Non-Toxic and Non-Irritant, devoid of leachable impurities, not retard disintegration time of the film, tasteless, should have good wetting and spreadability property, should exhibit sufficient peel, shear and tensile strength, readily available, inexpensive, should have sufficient shelf life, should not aid in causing secondary infections in the oral mucosa or dental regions. [12] Hydrophilic polymers can be biocompatible and have hence pulled in broad consideration in biomedical and drug delivery applications. They can be tailor-structured at both the molecular level and the gadget level. Significant applications in the biomedical field have been found by Hydrophilic polymers. [13] Now a day, both natural and synthetic polymers are utilized for the preparation of fast mouth dissolving film.

Film-forming polymers used in OTFs

The selection of polymers is one of the most critical and important parameters in the successful preparation of oral films due to their tensile strength, which depends on the type and amount of films used.[14,15] According to the total weight of the dry film, at least 45% polymer by weight must be present, but 60%-65% by weight of the polymer is chosen to achieve the desired properties. Polymers can be utilized alone or in combination to achieve the desired film properties. Because OTFs are rapidly dispersed and dissolved in the oral cavity, the film-forming polymers utilized must be water-soluble. [16]

Properties of an ideal polymer for OTFs are the following

The polymer used must be nontoxic and non-irritating

- There should not be impurities
- It must have enough wetting and spreading properties
- It must have sufficient stress and tensile strength
- It should be accessible and not too expensive
- The shelf life should be reasonable
- It should not cause secondary infections in the dental areas or oral mucosa
- It should have a good feeling in the oral cavity
- It must not be an impediment to the disintegration of time.[17]

Different polymers are utilized for the preparation of fast dissolving oral film. Some of them of natural polymers are discussed beneath together with their physicochemical properties and film forming capacities.[18]

Natural polymers

Because of cost efficacy and regulatory acceptance natural gums are the most popular hydrophilic polymers.[19]

Advantages of Natural Polymers[20]

1. As the name indicates they are available in nature so that they are Biodegradable in nature, and they are produced by all living organisms. All of these plant materials are reiterating sugar polysaccharides these are biocompatible and nontoxic.
2. When compared to synthetic materials cost of production is less for natural polymers. Large quantities of natural polymers are produced due to simple production processes are involved.[21]
3. Minimum chance of adverse and side effects with natural polymers when compared with synthetic Materials.
4. There is promotion being done by government for the plant production as pharmaceutical excipients, and it withal provides the facilities for bulk production, because of their wide applications like gum and mucilage's in industries In India and homogeneous developing countries.[22]

Natural polymers are various plant based materials. Plant-based material serves as an alternative to synthetic products because of different reasons:

I. Local obtainability
II. Ecological in nature
III. Bio-acceptability
IV. Having renewable source as well as lowest price when compared to synthetic products.[23]

Guar gum

It is also called guaran, is a galactomannan with high molecular weight of 8,000,000. It is obtained from the Guar plant as an endosperm seed Cyamopsis tetragonoloba (L) Taub. (Syn. Cyamopsis psoralioides).[24] It is free flowing, consummately soluble, neutral polymer which is composed of sugar units and has also been approved for use in food. Guar gum and derivatives are used as binders and disintegrate in films and also used as a control released agent for the drug. It is used in a concentration of 1% w/w as a disintegrant for the preparation of oral films.[25]

Mangifera indica gum (MIG)

In various pharmaceutical formulations MIG is used as a disintegrating agent, binder, suspending agent, and emulsifying agent because of it's non-toxic nature. It is used as a polymer in formulation of oral films.[26]

Pullulan

Pullulan is a natural and extracellular microbial polysaccharide produced by the fungus-like yeast, Aureobasidium pullulans. Pullulan can be made into very thin films (down to 0.01mm) which also have more tensile strength and can stable over a range of temperatures. Pullulan can be made into films of high tensile strength and low oxygen permeability, are oil and grease resistant. Pullulan films are usually prepared with 5-10% aqueous pullulan solution by rapid evaporation and applied to a smooth surface and dried; it may also involve the use of high temperature and pressure. Pullulan can be mixed with gelatin, amylose and polyvinyl alcohol for better release of drug.

Gelatin:

Gelatin is set up by the thermal denaturation of collagen, detached from animal skin, bones, and fish skins.18 Gelatin is a conventional term for a blend of filtered protein divisions acquired either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen and additionally may likewise be a blend of both. The protein parts consist for the most of amino acids consolidated by amide linkages to form linear polymers. 12 Mammalian gelatins ordinarily have better physical properties and thermo stability than most fish and this has been connected for the most part to their higher amino acid substance. There is the utilization of mammalian gelatin in the elaboration of palatable film or coating. [27]

Sodium Alginate:

Alginate is an indigestible biomaterial. Primarily sodium alginate comprises sodium salt of alginic corrosive, which is a blend of polychronic acids made out of deposits of Dmannuronic acid and L-guluronic acid. Palatable films made from alginate structure solid films and show poor water resistance because of their hydrophilic nature. A blend of starch and alginate to form edible film improves the mechanical properties of the film.

Pectin:

Pectin is a heterogeneous gathering of acidic polysaccharides. This complex anionic polysaccharide is made out of β-1,4linked d-galacturonic acid residues, wherein the uronic acid carboxyl are either completely (HMP, high methoxy gelatin) or in part (LMP, low methoxy gelatin) methyl esterified. With Chitosan, HMP or LMP forms magnificent films. To be sure, the cationic nature of chitosan offers the likelihood to exploit the electrostatic interactions with anionic polyelectrolytes, for example, pectin.

Starch:

Biopolymer starch is made out of glucose units and having two fundamental constituents are amylose and amylopectin.The starch got from various sources has a varying quantity of amylose and amylopectin normally 16- 28% of amylose content in starch granules, though waxy starch exclusively contained

amylopectin. Starch observed in nature in three principle crystalline allomorphs assigned as A, B, and V-type. B-type crystalline is quickly formed by amylose rich starch films and gradually by the aging of amylopectin rich starch films. Amylose is liable for the filmforming ability of starch.[28]

Starch mostly or completely replace plastic polymer. The films are see-through or translucent, flavorless, tasteless, and colorless. Films of high-amylose corn starch or potato starch were progressively stable during aging, lost little of their elongation, and had not or a slight expansion in tensile strength. Lycoat NG 73 is a magnificent film-forming polymer from pea starch. Lycoat is a novel granular hydroxypropyl starch polymer. Lycoat scatters easily in cold water without the development of lumps. [29]

Maltodextrin:

Maltodextrin is effectively digestible, being retained as quickly as glucose. Maltodextrin is ordinarily made out of a mixture of chains that differ from three to seventeen glucose units long.

Chitosan:

Chitosan (β-(1, 4) - 2-amino-2-deoxy-D-glucopyranose), which is chiefly produced using crustacean shells, is the second most abundant natural and non-poisonous polymer in nature after cellulose.[30]

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