

FORMULATION AND IN VITRO EVALUATION OF FAST DISSOLVING ORAL STRIPS

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Abstract

Fast dissolving oral strips (FDOs) are thin films that are laid on the tongue, where saliva hydrates them and they release the medicine into the oral cavity without the need for drinking water. They suggest a suitable method, particularly for individuals who cannot ingest medication orally, as well as for the general population. Because of the extensive network of small blood vessels in the mouth lining, drugs can quickly enter the bloodstream without passing through the liver, which enhances bioavailability and reduces adverse effects caused by first metabolism. This review covers the physiological and anatomical features of the oral cavity, permeation through the mucosa, and the biopharmaceutical aspects, important features, advantages and limitations of FDOs. The choice of drugs, the natural and synthetic polymers used, and the physico-mechanical properties of films, including tensile strength, elongation at break, Young's modulus, strain and glass transition temperature, are discussed. The influence of plasticizers, oral mucosal permeation enhancers, film formation from solutions containing water and the minimum film-formation temperature are also described, together with the materials PVP, PVA, glycerol, ethanol and menthol.

INTRODUCTION**Oro-Mucosal Drug Delivery****Oral Cavity Physiological and Anatomical Features**

The components of the oral cavity include the lips, tongue, cheeks, mouth, palate, and teeth. The coating of the mouth cavity is discussed to the oral mucosa. It has an over-all area of 200 cm² and is enclosed by a layer of laminated squamous epithelium [1]. The oral mucosa can be classified into three kinds: specialized mucosa (15%), masticatory mucosa (25%), and lining mucosa (60%) [2]. The masticatory mucosa covers the hard palate and gingival areas and is periodically coated with orthokeratin. Its cells are devoid of nuclear remnants and possess a high level of resistance to penetration [3]. The lining mucosa is found on the cheeks, lips, floor of the mouth, ventral surfaces of the tongue, and soft palate. The coating mucosa envelops the striated muscle at the lips, cheeks, and tongue, while it covers the glands at the soft palate, cheeks, and lower part of the tongue. Typically, this epithelium lacks keratinization,[4]. The lower surface of the tongue is the only area where specialized mucosa is found. The surface of the structure is composed of both keratinized and non-keratinized epithelium. Additionally, it contains taste buds and papillae. The presence of neutral lipids in keratinized epithelium makes it relatively impermeable to water, while non-keratinized epithelium has higher permeability due to lower levels of these lipids [5].

The salivary glands are accountable for the synthesis of both saliva and mucus. The pH of saliva varies between 5.5 and 7.4. Mucus is composed of proteins and carbohydrates and forms a protective layer on the cells of the mouth's lining. It carries a negative charge at the pH level that is optimal for normal bodily functions. Saliva decreases the resistance between the soft tissues in the mouth. Following an eruption, it facilitates continuous mineralization of the tooth enamel. The daily production of saliva varies between 0.5 and 2 liters [6].

The lamina propria, a dense and uneven tissue, has an extensive network of capillaries and blood

vessels. It supplies nutrients to the upper avascular epithelium as a result.

Permeation Through Mucosa

The trans-mucosal permeability in the mouth cavity is estimated to be four-four thousand times higher than that of the skin. The order of permeation based on the thickness and keratinization of these locations is as follows: sublingual > buccal > palatal. Transcellular and Paracellular paths are the primary routes for passive drug passage over the oral mucosa. Hydrophilic medications can easily pass across the intercellular gaps and cytoplasm due to their hydrophilic nature [7]. Lipophilic medications can easily pass through cell membranes due to their lipophilic nature. Furthermore, the oral mucosa has a tolerance for possible allergens due to its abundant blood supply, robust and rapid healing response following stress or injury, and lack of Langerhans cells. The primary constraint of oral mucosa is its low flow, thereby necessitating the use of a suitable permeation enhancer in most cases [8].

The Concept of Fast-Dissolving Oral Strips

There are multiple pathways for medication administration. The most commonly used administration routes include oral, parenteral, transdermal, and sub mucosal. According to results, the oral route is the furthestmost extensively approved method for administering drugs. More than 70% of drug traffic falls into the oral dosage form category. The high adaptability of oral dose forms is attributed to their inherent ease of use [9]. When medicine is taken orally, the total cost of treatment is relatively lower compared to other methods, and the patient is able to take the drug independently. However, around population 50 percent refrains from using solid oral dose procedures, such as capsules and tablets, due to the risk of oro-pharyngeal congestion. As a result, patients may decline to take oral medications [10].

The current advancement in delivery of drug schemes purposes to improve the safety,

protection & effectiveness of dose forms which are appropriate for patient adherence as well as administration. The administration of oral drugs has evolved from standard solid dosage forms to adapted release capsules / pills, flash release tablets, and eventually strips that dissolve swiftly in the mouth [11]. These FDOSs dissolve quickly when inserted in the mouth, releasing the medicine into the oral cavity without the need for drinking water. They suggest a suitable method, particularly for individuals who cannot ingest medication orally, as well as for the general population [12]. When these oro-dispersible strips are made with substances that promote the permeability of the oral mucosa, additional benefits are observed compared to standard enteral and parenteral formulations [13]. Because of the extensive network of small blood vessels in the mouth lining, drugs can quickly enter the bloodstream without passing through the liver. This method enhances the bio-availability of medicines administered orally that experience significant hepatic processing before entering systemic circulation. Therefore, it offers the shortest time for the drug to take effect, increased absorption into the body, and reduced chances of adverse effects caused by the first metabolism, resulting in greater patient compliance [14].

FDOSs, or thin films, are delivered by laying them on the tongue. The saliva hydrates the films, causing them to release the medicine. These films have a size and shape that is nearly undistinguishable to a postage stamp. These strips have received approval for prescription use in the United States, Japan and European Union [15]. The market for oral films is expected to experience significant growth and surpass other oral preparations containing the same active ingredient.

Biopharmaceutical Aspects

Fast-dissolving oral films (FDOSs) rapidly disintegrate and enhance the uptake of drugs through the esophagus and oral mucosa, pharynx. The key factors influencing drug absorption include age, the oral cavity environment, and blood flow to the buccal

region [16]. The physicochemical features and pharmacokinetics of each active salt are unique, which means that the distribution and duration of action mostly rely on the specific characteristics of the drug. Various medicines can be considered for these films, but those with smaller doses are better suitable.

Important Features of FDOSs

Mouth-dissolving films should possess a non-adhesive texture, be user-friendly in terms of dosage administration, be effortless to handle, and be suitable for labeling and packaging. The tablets should rapidly absorb moisture and dissolve between 1 and 30 seconds upon contact with saliva, allowing for the medication to be released [17]. The tablets must be non-obtrusive and specifically constructed to minimize deposit in the mouth after breakdown additionally, they should deliver a highly enjoyable tactile experience. The surface area can reach a maximum of 25 cm².

Compensations

The oral cavity has a surface area that is ample for the quick breakdown and absorption of fast-dissolving films. The oro-dispersible tablet (ODT) prescription is similar to mouth dissolving films in terms of quick release. However, ODTs are more brittle and fragile, necessitating specific packaging and handling procedures [18]. However, oral dissolving films possess flexibility, making them highly portable and simple to handle. Therefore, they outperform rapid dissolving pills in this regard.

Oral liquid formulations exhibit a faster onset of action compared to traditional solid dosage forms. However, when in the form of oral films, the dosage is more precisely determined. These dosage forms are ideal for dysphagic patients because they do not require swallowing. These films instantly dissolve in the mouth without requiring water, making them convenient to use anywhere as needed. These can also be simply supplied to people who are unconscious or resistant [19].

When mouth-dissolving films disintegrate in the mouth, the medicine can enter the systemic circulation and bypass hepatic metabolism because of the high blood vessel density in the buccal mucosa. This enhances the bioavailability of medications that undergo significant hepatic metabolism to a certain degree [20]. When the bioavailability of a medicine is enhanced, the dosage is reduced in order to achieve therapeutic blood levels and minimize the likelihood of side effects associated with dosage. The product has the potential to serve as a substitute that offers additional clinical advantages. Mouth-dissolving films are more cost-effective than many other dosage forms with equivalent effectiveness [21, 22].

Limitations

For drugs with higher doses, it is not possible to create mouth-dissolving films. The material homogeneity is the primary factor influencing the formulation of these films. The hygroscopic properties of the drug may also pose a problem. To ensure safety and stability, special packaging is required [23].

Basic Considerations of FDOs

Choice of Drugs for FDOs

The medications that can be produced in the FDOs should possess certain features. The taste of a medicine is a crucial factor to consider. If something is unpleasant, it is necessary to conceal or hide it. The second most crucial factor to consider is the dosage. Candidate medications must exhibit high solubility and stability in both aqueous solutions and saliva [24]. It is recommended that they maintain partial unionization at the buccal pH and exhibit strong penetration through the lining of the oral mucosa.

Since concentration affects polymer dissolution, film polymer concentration must be carefully chosen. This is why the films are very thin, as they cannot accommodate an excessive amount of medication. These strips have a lower drug loading capacity, which means that only medications with lower therapeutic doses and

small molecular weights can be made into mouth-dissolving films. In this respect, the films can individual accommodate a drug content ranging from 5 to 30% (w/w) [25]. This rapidly disintegrating formulation contains hydrophilic drug molecules in a dissolved state or in a solid solution. However, it will be disseminated throughout the polymer matrix film, if the drug is lipophilic. The drug release profile and satisfied homogeneity of the films may be improved through modifying the drug molecules to boost solubility, for example, through processes like milling, micronizing, or integrating them into nanoparticles [26]. Researchers should look into drug candidates that are meant to be buccal to see if they can irritate the oral mucosa and cause any local or systemic allergic reactions or bad effects on the oral cavity [27].

Oral films may be utilized to produce a diversity of over-the-counter (OTC) pharmaceuticals, including anti-allergic medications, cough suppressants, drugs for anti-asthmatics, erectile dysfunction, medications for gastrointestinal problems, anti-emetics, painkillers, and central nervous system (CNS) drugs such as those used for Parkinson's disease. Additionally, certain vitamins, central nervous system stimulants, and sedatives are also produced in facilities known as FDOs [28]

Polymers

The film properties of FDOs are solely determined by the polymer utilized in film preparation. The polymer is the fundamental building block of the film and constitutes 20–75% by weight of the total dry weight. Because of its high significance, the selection of the proper polymer is a critical limitation in the design of mouth-dissolving films. An optimal polymer for mouth-dissolving films should possess a strong attraction to water, exhibit quick disintegration in a watery environment, provide a pleasant sensation in the mouth, and possess suitable properties for producing a film. In order to address the challenges posed by environmental and transportation dangers, it is essential for these films to possess adequate mechanical

qualities, including appropriate tensile strength. The qualities of the films are primarily influenced by the characteristics of the polymers used, as well as the solvent and other additives [29].

The polymers commonly employed in the formulation of mouth dissolving films can be categorized into two groups: natural polymers,

such as cellulose derivatives, starch derivatives, polysaccharides, peptides and natural gums; and synthetic polymers, including polyvinyl Pyrrolidone, polyvinyl alcohol, polyethylene glycols, polyacrylic acids and carboxyvinyl polymers as represented in Table 1 [30].

Table 1: List of the polymers used in FDOs, along with briefed description of film characterization

Type	Name	Characteristics	References
Natural	Starch	The films are plain, tasteless, clear, and see-through, but they don't have much mechanical strength. Most of the time, plasticizer is needed to make the film stronger.	[31]
Natural	Pullulan	Have great mechanical qualities, don't taste or smell, are clear, flexible, heat-sealable, and highly oxygen-impermeable, and dissolve easily in water.	[32]
Natural	Gelatin	More stable gelatin makes better pictures. Gelatin films break down quickly, hold tastes well, and leave a pleasant taste.	[33]
Natural	Sodium alginate	Tough, but prone to hygroscopy; have low mechanical strength that can be raised by adding starch.	[34]
Synthetic	Hydroxypropyl Methylcellulose (HPMC) (low viscosity grades e.g; E3,E5,E15)	HPMC forms clear, stiff and elastic films from aqueous solutions.	[35]
Synthetic	Hydroxypropyl Cellulose (HPC)	Because the Tg was high, the films that were made were stiff, had a high stiffness of elasticity, and stretched less than 1%.	[36]
Synthetic	Sodium carboxymethyl Cellulose (Na-CMC)	Have high drug loading ability.	[37]
Synthetic	PVP - Polyvinyl Pyrrolidone	Brittle in nature so cross povidone is mixed to synthesis elastic films.	[38]
Synthetic	Polyvinyl Alcohol (PVA)	Have good tensile strength and flexibility, good resistance to oxygen and smells, and a short dissolution time.	[39]

Physico-Mechanical Properties of Films

Mechanical Properties

The film's mechanical strength is demonstrated by specific metrics, namely percent elongation at break (EB), Young's modulus (YM) of elasticity, tensile strength (TS), and strain. Strain refers to the measure of deformation in a body, specifically the relative displacement of particles, excluding rigid-body motions [40]. This deformation occurs when stress is applied, either through changes in temperature or the application of force. The strength and elasticity of films increase with higher strain values [41]. Tensile strength is the highest level of stress that a substance can endure when subjected to stretching or pulling forces prior to failure or fracture. The quality in question is solely attributed to the substance and

is therefore unaffected by the size of the test sample. However, temperature does have an impact on materials' tensile strength, as it is one of the elements that determines their mechanical properties [42].

YM refers to the measure of a material's tendency to undergo elastic deformation when subjected to an external force. Elongation at break refers to the highest level of distortion or strain that a material can undergo before it breaks. The term "stiffness" refers to the measure of the resistance of a material to deformation [43].

Figure 1 shows a graph that can be used to group different types of polymers based on their stress and strain. For a picture, the TS, EB, and strain should all be high, but the YM should be low.

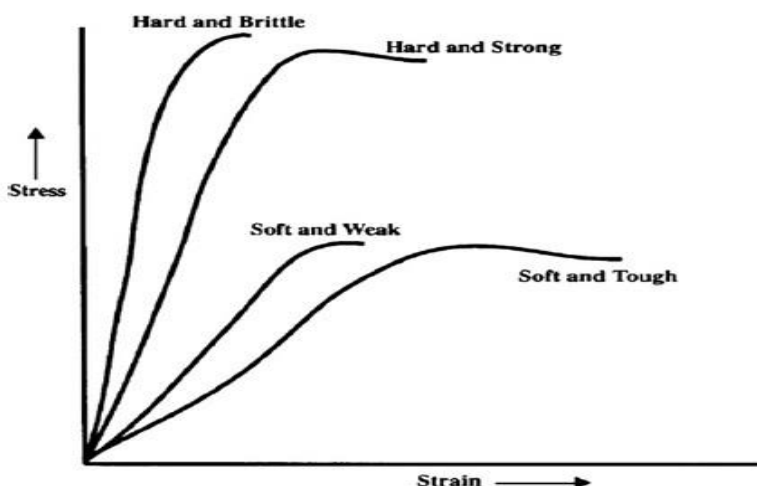


Figure 1: Effect of type of polymer on stress and strain

Glass Transition Temperature (T_g)

It refers to the specific temperature at which the delicate polymer starts to soften on the thermal scale. T_g, or glass transition temperature, is influenced by various factors associated with the molecular structure of the polymer [44]. Some of these factors are the polymer's backbone chain, the number and location of functional groups, their polarities, and the polymer's overall molecular weight. This is the reason why the T_g numbers of different grades of the same polymer are different.

According to literature, films made from polymers with low glass transition temperature (T_g) exhibit elasticity, high elongation at break (EB), and a lower elastic modulus [45]. However, polymers with exceptionally high glass transition temperatures (T_g) result in films that lack flexibility, possess a high elastic modulus, and have poor elongation at break (EB). The study of polymers' physico-mechanical properties demonstrates how important these factors are when selecting polymers for oral strips that dissolve quickly.

The Influence of Plasticizers on the Properties of Polymeric Films

A plasticizer is typically a small organic solvent with a glass transition temperature ranging from -50 to -150 °C. Plasticizers are essential ingredients that have the ability to alter the film's characteristics [46]. When applied at the correct concentration. They have the ability to transform a rigid and delicate film into a pliable and more robust one. Widely utilized plasticizers include polypropylene glycol (PPG), polyethylene glycol (PEG), sorbitol and glycerol. The amount of plasticizer in a film is determined by the polymer type utilized, and it can range 0%-50% of polymer weight and 5-20% by film weight [47].

Mechanism of Plasticization

The positive impact of plasticizers may be explained by the collaboration between polymer chains and the plasticizer molecules. Plasticizer molecules intervene by disrupting the connections between polymer chains. By employing this method, they induce spaces between polymer molecules, resulting in the formation of a polymer-plasticizer compound [48]. By adding a plasticizer to the polymer, the film's elastic modulus and glass transition temperature go down. This makes the film more flexible. Plasticizer molecules infiltrate the amorphous regions of the polymer without modifying its crystalline structure [49].

Comparison of Different Plasticizers

A study was conducted to examine the impact of various plasticizers including PEG 400, PEG 1450, PEG 8000, and PEG 20000, PG, and glycerol) on the composition of methyl cellulose films. With the exception of PG, all plasticizers led to a decrease in tensile strength [50]. The most significant decrease was observed with PEG. Apart from PEG 400 and PG, all other plasticizers enlarged the percentage elongation range of the methylcellulose films. The highest elongation was observed with PEG 1,450. Overall, PEG and glycerol were found to be the furthestmost effective plasticizers for methylcellulose [51, 52].

Concentration of Plasticizer

The polymer's puncture strength decreases with the optimal concentration of plasticizer. Rising the concentration of plasticizer leads to rise in moisture retention by the polymer, which is the main reason for the flexibility in films containing plasticizer [53]. A 68% increase in the flexibility of five percent hydroxypropyl cellulose films was detected when the plasticizer concentration was enlarged in the range of 1-3%. Therefore, the mechanical possessions of films polymer may be controlled by adjusting its plasticizer [54].

Limitations with the Use of Plasticizers

Despite numerous benefits, plasticizers can have a significant downside. Plasticizer-containing films are more susceptible to oxidative and hydrolytic destruction because they have a higher permeability to oxygen and moisture. Therefore, it is necessary to use suitable packaging for the strips [55].

Permeation Enhancers (Oro-Mucosal**Permeation)**

Permeation enhancers are extensively investigated for buccal dosage forms because the buccal mucosa has lower permeability compared to the intestinal epithelium. In order to be considered a successful show, it is essential that the substances used have minimal or no harmful effects on the tissue of mucosal. The process for the molecules of drug passing by mucosa is explained through passive diffusion [56]. The process of passive diffusion could be explained using "Fick's law of diffusion" [57], represented as:

$$J_{ss} = (D \cdot K / h) \cdot CD \quad (1)$$

The equation clearly shows that the "steady state flux (J_{ss})" is linked to the k which is partition coefficient, CD is the drug concentration in the internal compartment side and D shows the diffusion constant. On the other hand, it is in reverse to the thickness (h) of the permeating membrane.

For a specific formulation, the medication concentration remains consistent. Permeation enhancement can be achieved by modifying either the diffusion coefficient (D) or the partition coefficient (K). It is evident that the

choice of a permeation enhancer is influenced by the physicochemical characteristics of the drug molecule [58].

Mechanism Behind Permeation Enhancement

It is typically function by augmenting the paracellular pathway of captivation across the mucosa. Surfactants like sodium dodecyl sulfate and sodium lauryl sulfate enhance permeability by removing lipids from the mucosa. Furthermore, bile salts facilitate the absorption of lipids through the extraction process. They achieve this by increasing the fluidity of intercellular lipids, such as sodium deoxycholate, which promotes the absorption of fatty acids. Additionally, bile salts disrupt the arrangement of intercellular lipids, leading to enhanced absorption of ethanol [59, 60].

Formation of a Film from Solutions Containing Water

The process of forming a film from polymer solutions is intricate. When in a solution state, polymer molecules are widely dispersed, but they must come into close proximity and bond together in order to form a film during the drying process. Throughout this process, water molecules gradually undergo evaporation while polymer molecules align themselves in close proximity [61]. The capillary action of water molecules around the polymer molecules causes evaporation. Discrete film formation happens when polymer molecules have the ability to undergo deformation and merge with one another. The illustration of this phenomenon can be seen in Figure 2.

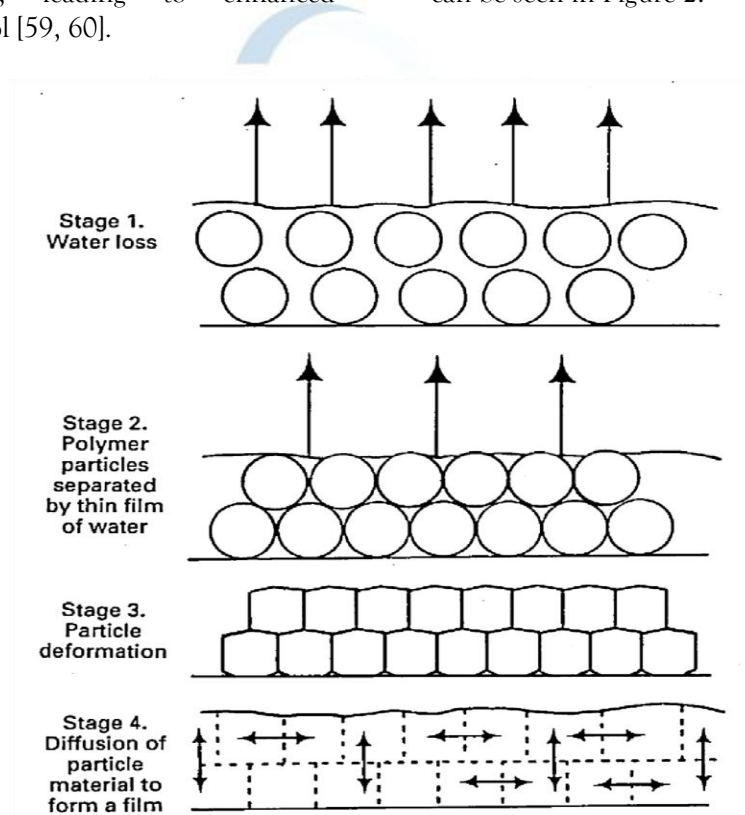


Figure 2: Film formation during drying process

Film Formation Minimum Temperature

The least temperature during formation of film happens under specific circumstances is referred to as the minimum film-formation temperature (MFT). The MFT is contingent upon the glass

transition temperature (T_g) of polymers. For aqueous dispersions of polymers, it is advisable to maintain a drying temperature that is at least 10-20 °C higher than the Minimum Film Formation Temperature (MFT) [62]. This allows water to

have its desired plasticizing effect. The addition of plasticizers to polymers can decrease their MFT by reducing their glass transition temperature.

Materials Used (Selection of the Polymers)

Polyvinyl Pyrrolidone (PVP)

It is alternatively referred to as Povidone, Kollidone, Polyvidone, and other names. It is a homopolymer of 1Ethenyl-2-pyrrolidinone. The substance exists as a loose, finely ground powder that is white to off-white in color and has the property of absorbing moisture from the air [63]. The compound has a structural formula (Figure

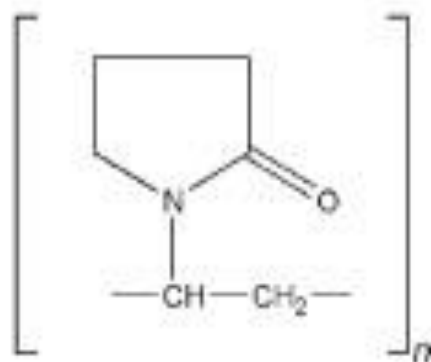


Figure 3: Structure of PVP

The molecular weight of PVP K30 is around 50,000. It exhibits complete solubility in all substances. It can dissolve in both water-loving (hydrophilic) and water-repelling (hydrophobic) solutions [66]. The relative viscosity of a 1% weight/volume aqueous solution of PVP K30 at 25°C was determined to be in the range of 1.201–1.281 using a capillary viscometer. The pH range of a 5% aqueous solution is between 3.0 and 5.0. According to Bühler (2005), a 10% w/v solution of PVP K30 is transparent [67].

When dissolved, it has remarkable wetting characteristics and easily creates thin layers. From a physiological standpoint, this polymer is compatible and does not cause toxicity or ionic interactions [68]. This is widely accepted because of its chemical, thermal, and pH stability. It

3) of $(C_6H_9NO)_n$ with a molecular weight that is between the range of 2500 and 3,000,000 [64]. The molecular weight of a substance is determined by its degree of polymerization and is measured using the K-value. The value of K is determined by the viscosity of the aqueous PVP solution in comparison to that of water. It is situated within the numerical interval of 10 to 120. Particles with grades equal to or less than K30 have a spherical shape, while particles with higher K values have a plate-like shape. It is either odorless or has a very faint odor [65].

functions as a solubilizer in both parenteral (administered through injection) and oral formulations. Tablets utilize it as a binder, which is incorporated during the wet granulation process.

Polyvinyl Alcohol (PVA)

It is alternatively referred to as Elvanol, Airvol, Polyvinol, Ethenol or vinyl alcohol polymer. The substance is a white to cream white powder along with a granular texture and no odor [69]. The molecular formula $(CH_2CHOH)_n$ is seen in Figure 4. For commercially accessible materials, the value of n typically falls within the range of 500 to 5000, corresponding to a molecular weight range of around 20,000 to 200,000 [70].

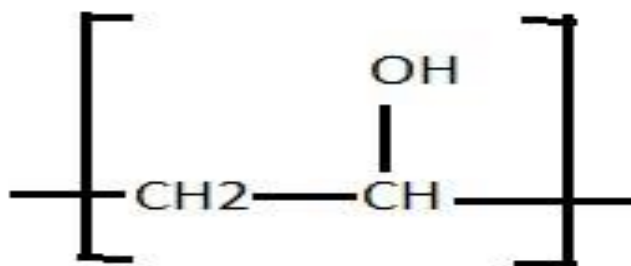


Figure 4: Structure of PVA

It dissolves in water, has limited solubility in pure alcohol, and does not dissolve in other organic solvents. To dissolve in water, the substance is dispersed in cold water and then heated to 90 °C while being stirred for 5 minutes. After that, it is cooled to room temperature while still being stirred [71]. According to study, the dynamic viscosity of a 4% weight/volume aqueous solution varies from 4 to 65 millipascal seconds at 20 degrees Celsius [72].

The PVA molecule has a two-dimensional structure that consists of a hydrogen-bonded network sheet. The physicochemical characteristics of PVA differ depending on the preparation procedure. Polyvinyl alcohol (PVA) exhibits the highest production rate among synthetic polymers due to its exceptional thermal and chemical durability, complete biodegradability, and ability to create films. It is considered safe for oral administration due to its non-mutagenic properties and lack of accumulation in the body. The glass transition temperature of PVA is 87 °C [73].

Glycerol

Glycerin is an alternative name for it. The chemical's nomenclature is Propane-1, 2,3-triol. The substance is a viscous, colorless liquid that is clear and hygroscopic, meaning it readily absorbs moisture. It does not have any discernible odor. It has a sweetness level that is 0.6 times lower than sucrose. The chemical formula of the

compound is $\text{C}_3\text{H}_8\text{O}_3$ and its molecular weight is 92.09 [74]. The structural formula is depicted in Figure 5. The compound exhibits solubility in water, methanol, and pure alcohol, with a lesser degree of solubility in acetone and ether. However, it is insoluble in oils, chloroform, and benzene. The dynamic viscosity of a 10% aqueous solution at 20 °C is approximately 1.311, and 1.024 is specific gravity. It is utilized as a emollient and humectant in topical remedies, a solvent, sweetener, antibacterial agent, and viscosity enhancer in oral solutions, and a plasticizer in polymeric films [75].

At room temperature, it remains in a stable liquid state, but it undergoes decomposition when subjected to heat. If held at low temperature, it has the potential to undergo crystallization. It is recommended to store it in containers that are airtight [76]. The material exhibits glass transitions at low temperatures. The glass transition temperature of the material is - 83.15 °C [77]. Glycerol is the most commonly utilized plasticizer among polyhydric alcohols. Because of its hygroscopic properties, it absorbs water from the atmosphere to enhance the plasticization effect. Comparatively, it has been demonstrated that this substance exhibits greater hygroscopicity and has a stronger plasticizing impact in starch films, in comparison to xylitol and a 1:1 combination of glycerol and xylitol [78].

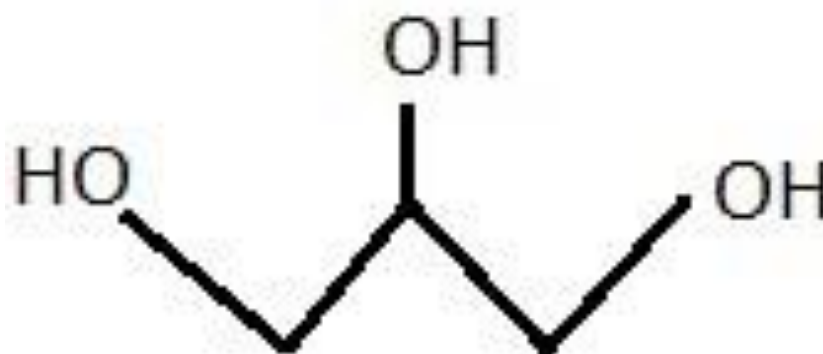


Figure 5: Structure of Glycerol

Ethanol

The absorption of peptides was facilitated by ethanol at different doses, specifically 5% and 30%. An enhancement in the permeability of caffeine through porcine buccal mucosa was reported following pretreatment with ethanol. Ethanol enhances permeability by disrupting the regular arrangement of lipid molecules [79].

Menthol

Hexahydrothymol is an alternative name for this compound. The chemical formula of the compound is $C_{10}H_{20}O$, and its molecular weight is 156.27 [80]. The figure displays the structural formula (Figure 6).

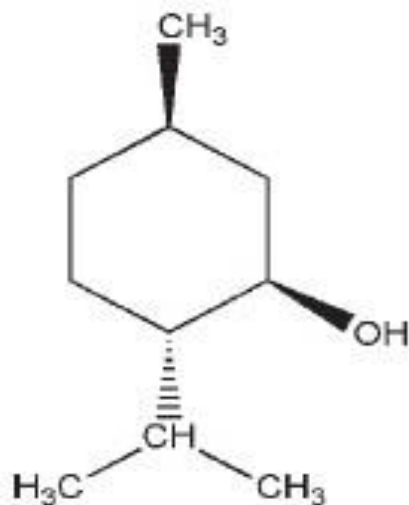


Figure 6: Structure of Menthol

The substance can exist as a powder that flows freely or clumps together in crystalline form. The crystals can be colorless, prismatic, or needle-like, and they may also appear as hexagonal or fused masses [81]. The substance has a distinct and powerful smell and flavor. It exhibits high solubility in ethanol (95%) and low solubility in

water. It is advisable to preserve it in well-sealed ampules at temperatures below 25 °C to avoid the process of sublimation that occurs at higher temperatures.

Menthol is commonly employed as a flavoring ingredient in pharmaceutical preparations and confectionery. In order to provide flavor to

tablets, they are initially dissolved in ethanol. Additionally, it is utilized as a permeation enhancer due to its ability to stimulate the dilatation of nearby arteries. The dilatation of blood vessels is responsible for the cooling and pain-relieving action of menthol [82].

Conclusion

FDOSs dissolve quickly when inserted in the mouth, releasing the medicine into the oral cavity without the need for drinking water, which makes them a suitable method for individuals who cannot ingest medication orally. Because of the high blood vessel density in the buccal mucosa, the medicine can enter the systemic circulation and bypass hepatic metabolism, which enhances the bioavailability of medications that undergo significant hepatic metabolism. FDOSs have a lower drug loading capacity, so only medications with lower therapeutic doses and small molecular weights can be made into mouth-dissolving films, and special packaging is required to ensure safety and stability. The film properties are determined by the polymer utilized in film preparation, and the selection of the proper polymer is a critical limitation in the design of mouth-dissolving films. Plasticizers such as glycerol can transform a rigid and delicate film into a pliable and more robust one, and the mechanical properties and glass transition temperature of the polymers are important factors when selecting polymers for oral strips that dissolve quickly.

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