INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Sumatriptan Succinate Loaded Oral Films For Potential Treatment Of Migraine: In Vitro Study

Sandhra S.*, Roopesh P. T., Anagha Mohan, M.Roshni, Megha V. S., Haritha K., And Sindhu V.

Department of pharmaceutics, Rajiv Gandhi Institute of Pharmaceutical Science and Research, Kasaragod, 671310

ARTICLE INFO

Received: 26 July 2024
Accepted: 29 July 2024
Published: 31 July 2024

Keywords:
Sumatriptan succinate, fast dissolving films, Antimigraine.

DOI:
10.5281/zenodo.13137462

ABSTRACT

Sumatriptan succinate is an anti-migraine drug that is structurally similar to the serotonin and can induce the activation of 5HT receptor. Sumatriptan succinate is the first member of a new class of antimigraine compounds that act as a specific and selective 5-hydroxytryptamine-1 receptor agonist. Primarily due to presystemic first-pass metabolism and partially due to inadequate absorption, sumatriptan succinate has a reduced bioavailability. Oral route of medication is a most favoured dosage form because of its simplicity of organization, non-obtrusiveness, flexibility, patient consistence and agreeableness. Fast dissolving films are the advancement in the solid dosage forms and having more patient compliance. Advances in formulation technology have led to the development of various intraoral dosage forms and among them fast dissolving drug delivery systems (FDDDS) have gained popularity in recent years. This review highlights the various types of polymers, the different methods for the preparation of fast dissolving films and evaluation tests for the oral films.

INTRODUCTION

The most popular and fastest-growing method of administering drugs is orally. The film or strip provides rapid local and systemic drug release within seconds or takes few minutes by varying rate of dissolution. Fast dissolving oral film is a new dosage form and is termed as a thin film drug delivery system or quick dissolving delivery system. In this study the development of fast dissolving film prepared by the combining of different polymers concentrations. Various film forming polymers like Hydroxyl propyl methyl cellulose E15 and E3, polyvinyl pyrolidone and polyethylene glycol 400 and sodium carboxyl methyl cellulose are used. Sumatriptan succinate is an anti-migraine drug is structurally similar to

***Corresponding Author:** Sandhra S.
Address: *Department of pharmaceutics, Rajiv Gandhi Institute of Pharmaceutical Science and Research, Kasaragod, 671310*
Email : sandhras303@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

the serotonin and can induce the activation of 5HT receptor .Fast dissolving drug delivery system were first developed in late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experienced difficulties in swallowing traditional oral solid dosage forms[1]..

Oral route is the best route for the administration of drug. Sumatriptan succinate, 5HT1B/1D receptor agonist in the triptans class is used to treat migraines. The lower bioavailability of sumatriptan succinate is primarily because of presystemic first pass metabolism and partly because of incomplete absorption[2]. A mouth dissolving film serves as a drug delivery system that quickly disintegrates and dissolves in the oral cavity to release medication for absorption in the mucosal and intragastric areas without the need of water intake. Sumatriptan succinate has a low oral bioavailability of 15% because of its extensive first-pass metabolism. Additionally, a significant number of patients experience severe nausea or vomiting during their migraine attacks, rendering oral treatment of sumatriptan succinate inadequate2.

- The nasal and subcutaneous routes both have limitations. For example, nasal solutions have a shorter retention time, and injectable preparations cannot be self-administered. The development of an efficient formulation is necessary to enable the drug to enter the systemic circulation directly, bypassing the initial metabolism. This will ultimately increase the bioavailability of sumatriptan succinate

Methods for the preparation of buccal film

- Solvent casting.
- Hot melt extrusion.
- Semisolid casting.
- Solid dispersion extrusion.
- Rolling methods

Solvent casting method

The drug is dissolved or suspended in a solution that contains polymers, plasticizers, and other excipients, which are dissolved in a volatile solvent such as ethanol or water. This mixture is known as film dope, and it is subsequently poured into a petri plate and processed through drying equipment, such as an oven, to eliminate all the volatile solvents. The resulting dried film is then cut into strips using a die and placed into sealed pouches.

Hot melt extrusion

In HME, the polymer is melted, the API is added, and the mixture is then extruded through a die to create a film. This is a continuous production procedure

• Steps:

1. Melting the polymer and plasticizer.
2. Combining the molten polymer with the API.
3. The oral film is prepared using the spray drying process.
4. Creating a thin film by extruding the mixture through a die.
5. Cooling and solidifying the film.
6. Cutting the film into the desired shape and size

   The extruder conveys, mixes, and melts the drug polymer combination after it has been filled in the hopper. A die forms the melt into the desired shape. This technique uses a drug polymer mixture that has a shorter residence time (less than two minutes) and a lower temperature. This process uses no organic solvents and can run continuously with very little waste of product3.

Semi solid casting method

Is a casting technique where an alloy with two phases the alpha phase, which has a higher melting point than the eutectic is stirred between the liquid and solid phases at a predetermined temperature. The metal is filled into the mold while it is partially molten, distributing solid globules evenly throughout the liquid.

Solid dispersion extrusion

The term "solid dispersion" describes the dispersion of active substances in the presence of amorphous hydrophilic polymers in a solid form within an inert carrier. The medication is dissolved in an appropriate liquid solvent, and then the liquid solvent is added to the polyethylene glycol melt at a temperature lower than 70C without draining the solvent. And the solid dispersions are passed through dies to shape them in form of film4.

Rolling method

Using two rollers, a combination of polymer, plasticizer, and API is rolled out to create a thin film.

• Steps:

1. Mixing the polymer, plasticizer, and API to form a uniform dough-like mass.
2. The dough is fed between two rollers that are near to one another.
3. Adjusting the gap between the rollers to achieve the desired film thickness.
4. Cutting the film into individual doses.

Using the rolling process, a pre-mix is made, to which the active medication is subsequently added to create the film. Film-forming polymer, polar solvent, plasticizer, and other excipients are included in the pre-mix batch; the medicine is added to the master batch. To ensure uniformity, the needed amount of the master batch and premix are pumped into separate containers, and the drug is then blended with the master pre-mix for a predetermined amount of time. After the mixture is thus created, it is fed into the roller. The metering roller applies the mixture to the roller and regulates its thickness. After the film is produced, the support roller removes it. Second metering pump feeds a certain amount of matrix into pan. The metering roller measured the thickness of the film. Finally, the film forms on the substrate and is removed by the support roller. It is preferable to prevent the presence of outside air during the controlled bottom drying process since the resulting film is moist when it is first created. Film is cut into various sizes and shapes based on requirements once it has dried5.

Definition of FDOF

An ultra-thin film containing active ingredients that dissolves quickly in saliva without the need for water or chewing is known as a fast dissolving oral film. Its rapid dissolution is attributed to its larger surface area and thinner profile compared to a tablet. The film, made of hydrophilic polymers, quickly dissolves when in contact with saliva in the oral cavity. This allows for the rapid release of the drug into the saliva, where it is then absorbed by the highly vascularized oral mucosal tissues. Developing formulations for children has presented numerous challenges, with the palatability of paediatric oral medications being a significant factor influencing adherence to therapeutic regimens. Elderly individuals and adolescents generally prefer solid dosage forms, while younger children favour liquid formulations for easier swallowing. Pharmaceutical research has focused on creating fast dissolving oral films (FDOFs) to improve administration and swallowing. The evolution of oral drug delivery has progressed from traditional tablets/capsules to modified release forms, oral disintegrating tablets (ODTs), wafers, and the recent development of fast dissolving oral films. The FDOF'S are essentially an extremely thin strip that is the size of a postage stamp and contains an active pharmaceutical ingredient along with other excipients. The convenience of dosing and the portability of FDOF'S have resulted in a broader acceptance of this dosage form among both the paediatric and geriatric populations. The introduction of FDOF'S in the market involved educating the public about the correct way to use the product, including providing instructions such as "do not swallow" or "do not chew".

Classification of Fast Dissolving Technology

Lyophilized systems

With the aid of a mold or blister pack, a drug suspension or solution combined with additional structural excipients is formed into tablet-shaped units by the technology underlying these systems. After that, the tablets or units are frozen and lyophilized inside the mold or pack. Due to their extremely high porosity, the resultant units dissolve and absorb water or saliva very quickly.

Compressed tablet-based systems

The production of this system involves the direct compression of excipients utilizing standard tablet technology. The hardness and friability of tablet technologies vary depending on the manufacturing process. Fast dissolve tablets dissolve more quickly than regular tablets because they are formulated with water soluble excipients, superdisintegrants, or effervescent ingredients that allow water to quickly enter the tablet's core.

Thin film strips

Oral films, also known as oral wafers, originated as breath strips in the confection and oral care industries and have since developed into a novel and extensively used delivery system for vitamins and personal hygiene products. FDFs are currently in the early to mid-development stages for prescription drugs and are a tried-and-true technology for the systemic delivery of APIs for over-the-counter (OTC) drugs. Customers have linked this to the success of breath freshener products like Listerine Pocket Paks in the US market. Such systems create a 50–200 mm film by using different hydrophilic polymers. The film is produced as a big sheet, which is subsequently divided into doses6.

Classification of Oral Films

Oral films can be divided into three categories:

- Flash release wafers
- Mucoadhesive melt away wafers
- Mucoadhesive sustained release wafers.

Packaging of oral film

In the pharmaceutical business, it is crucial that the package chosen maintains the product's integrity. Safeguarding the dosage of other rapidly dissolving dosage forms during manufacturing and storage necessitates costly packaging, particular processing, and extra caution. For fast-dissolving films, there are numerous packaging choices. Films are pharmaceutical products that must be packaged in singles; the most popular package type is an aluminium pouch. The Rapid card is a patented and exclusive packaging system created by APR-Labtec that is specifically made for the Rapid films. Three raid films are stored on each side of the credit card-sized rapid card. Each dose can be removed on its own.

The chosen material needs to possess the subsequent qualities:

- It needs to shield the preparation from external factors.
- The FDA has to approve them.

They have to fulfil the relevant requirements for tamper resistance. They have to be harmless. They can't react negatively to the product. They can't add flavours or scents to the product7.

Single pouch and Aluminium pouch

Peel-able soluble film drug delivery pouches have high barrier qualities and can dissolve quickly. For product display, the pouch is transparent. One side can be made clear and the other can be laminated with inexpensive foil by using a two-structure combination. There is almost no gas or moisture transmission through the foil lamination. The package offers a pharmaceutical and nutraceutical application a flexible thin film substitute. Product and dosage protection are both offered by the single dose pouch. A pouch made of aluminium is the most widely used type.

Foil, paper or plastic pouches

The flexible pouch packaging concept can offer a package with a high level of environmental protection in addition to being temperature-

resistant. During the product filling process, a flexible pouch is typically created using either vertical or horizontal forming, filling, or sealing equipment. Single or aluminium pouches are both possible for the pouches.

Blister card with multiple units

The blister and lid stock are the two parts of the blister container.The blister is the product-holding cavity that is formed, and the lid stock is the material that seals to the blister.The required level of protection should guide the choice of films.Typically, aluminium foil is used to make the lid stock.Usually, a plastic is utilized to create the cavity, and this material can be made to shield the dosage form from moisture.

Barrier Films

Since many medication preparations are highly susceptible to moisture, high barrier films are necessary. Moisture protection can be achieved with a variety of materials, including polypropylene.

Continuous roll dispenser

An automated medication cassette is a small reusable portable dispenser unit with a roll of drug tape, along with a metering and dispensing device, are contained within a disposable cassette. A measuring tool built into the dispenser allows you to precisely gauge the length of tape as it is dispensed. A counter keeps an eye on how many doses of medication tape are still in the dispenser. To notify the patient when it's time for the medication to be dispensed, a timer device might be offered. When the dispenser unit's lid is lifted, the measured length of medication a cutter blade built into the lid cuts the tape off of the roll. By modifying the length of the released tape, the patient can receive the prescribed medication in the appropriate dosage and administration8.

Advantages of oral film

- The drug is delivered by the buccal and sublingual film, which has the ability to increase the medication's safety profile, decrease its dosage, and accelerate its onset of action.
- The gastrointestinal tract is the main route by which all single unit dosage forms, soft gels, and liquid formulations enter the bloodstream. It is through this route that the drug is primarily broken down by bile, stomach acid, digestive enzymes, and other first pass effects. Because of this, these formulations typically have a delayed onset of action and need larger doses. However, these problems can be avoided by utilizing the current oral film drug delivery systems, which produce a quicker onset of action at lower doses.
- Comparing oral film to other traditional dosage forms, it dissolves more quickly and is more stable and long-lasting.
- Compared to liquid formulations, oral film allows for more accurate dosing because each strip is made to precisely contain the right amount of medication.
- Oral film guarantees more precise medication administration. Because oral film is so naturally easy to administer and has an intuitive dosage form, it can increase compliance. Patients with paediatric, geriatric, and neurodegenerative diseases, for whom accurate and comprehensive dosage can be challenging, can particularly benefit from these qualities. The ability of oral films to dissolve quickly without the need for water gives patients who experience nausea or dysphasia, such as those undergoing chemotherapy an alternative9.
- Oral film drug delivery may allow for the development of sensitive drug targets that are not feasible in tablet or liquid formulations. Oral film drug delivery technology presents commercial opportunity for pharmaceutical companies

that are facing generic competition and have an expiring drug patent. This technology can help these companies extend their revenue lifecycles.

- Sublingual film provides a quick-dissolving therapeutic dose in a waterproof, abuse-resistant film matrix that is rapidly absorbed under the tongue to guarantee compliance and cannot be crushed or injected by patients.

Disadvantages of oral film

- The amount of medication that can be included in each unit dose of oral disintegrating films is limited. Drug doses for lyophilized dosage forms should typically not exceed 400 mg for insoluble drugs and 60 mg for soluble drugs. Additionally, because of the nature of quickly dissolving oral films, fragile products require special packaging, which could raise the cost of the product10.
- Dose uniformity is a challenge.
- It takes moisture from atmosphere.
- For the stability and safety of the product, appropriate packaging is needed.

Overview of the oral cavity

The outermost layer of the oral mucosa is made up of stratified squamous epithelium. The basement membrane, lamina propria, and submucosa, the innermost layer, are located beneath this. In terms of permeability, the oral mucosa lies in the middle between the intestinal and epidermis mucosa. The buccal mucosa's permeability is thought to be 4–4000 times higher than the skin's. The various structures and functions of the various oral mucosa result in significant variations in permeability between the various areas of the oral cavity. The buccal cavity is lined with a mucous membrane which, like the lining of the entire alimentary canal, behaves as a lipoidal barrier to the passage of drugs. In general, by simple diffusion, they pass through the mucosal membrane and enter the bloodstream through the jugular vein, which carries them into the general circulation and amply nourishes the salivary glands and their ducts. Drugs are typically moved across the oral mucosa by active transport, pinocytosis, and passing through aqueous pores, all of which are rather unimportant processes. Many medications are only partly ionized at physiological pH, despite the fact that they are organic electrolytes in considerable quantities. If the unionized forms are lipid soluble, they can pass through the buccal membrane quickly, but the ionized forms are far less soluble in lipids and are thus more difficult to get through. Moreover, the charge on the ionized species might cause it to be repelled from or adsorbed onto the membrane surface, which has strong dipoles or charged groups, preventing the ionized form from passing through the membrane. Therefore, the amount of unionized medication and its lipid solubility will mostly dictate the rate of diffusion across the membrane. It is believed that passive diffusion via the buccal mucosal cell membrane causes buccal absorption11.

Factors affecting absorption

- Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids.
- Binding to the oral mucosa: There is a low level of systemic availability for medications that bind to the mouth mucosa.
- PH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favours the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- Lipophilicity of the drug.
- A medication must have a little higher lipid solubility than that needed for GI

absorption in order for passive permeation to occur and for the drug to be fully absorbed through the sublingual route.

- The thickness of the oral epithelium is smaller than that of the buccal layer, with the sublingual epithelium being just 100–200 μm. As a result, medications are absorbed more quickly because to thinner epithelium and less salivary volume immersion.

Buccal epithelium

The buccal epithelium is a stratified squamous epithelium that lacks keratinization. It is made up of several layers of cells with varying maturation patterns between the surface and deepest levels. As cells advance toward the surface, the buccal epithelium's basal cells can divide and keep the population of epithelial cells stable. Differentiation, followed by migration and desquamation of the surface cells, is necessary for tissue homeostasis. The prickle cells (intermediate layer) accumulate lipids and cytokeratin of low molecular weight that do not aggregate to form filaments. Membrane coating granules, also known as lamellar granules, are tiny organelles that contain an internal lipid component. Such granules migrate towards the apical surface of the cell, where their membrane fuses with the cell membrane and their lipid content is extruded in the extra cellular space12.

The buccal epithelium lacks tight junctions, which are common to intestinal and nasal mucosa, but is endowed with gap junctions, glydesmosomes and hemi desmosomes, which are loose intercellular links. The epithelium rests on the basal epithelium, an irregular saliva continuous interface between the epithelium and the connective tissue. The basal membrane anchors the epithelium to the connective tissue and improves the barrier function of the epithelium, preventing large molecules from passing through the oral mucosa. Although buccal absorption is not the specific goal of oral fast dissolving tablets, this can happen when a medication enters the oral cavity and comes into touch with the buccal mucosa.

There are two main pathways via which drugs are transported via the buccal mucosa:

• Transcellular (intracellular)

• Para cellular (intercellular)

Migraine

Migraine presents as a long-term neurological condition characterized by recurring, painful headaches often accompanied by symptoms like sensitivity to light and sound, nausea, vomiting, and other autonomic nervous system-related symptoms. This prevalent and incapacitating disorder affects 10-15% of the population, and its causes are not yet fully understood. Migraine attacks primarily stem from changes in the functioning of neurons containing 5-hydroxytryptamine (5-HT), leading to trigeminal system depolarization and the release of vasoactive neuropeptides. The most frequently prescribed type of medication for treating migraines is triptans, which work by constricting the blood vessels in the head and preventing the release of vasoactive neuropeptides13. The onset of a severe throbbing headache typically begins on one side, often accompanied by sensitivity to light, feeling nauseous, vomiting, and exhaustion, which can last for several hours. Visual disturbances before the headache occur in only about 20% of people with migraines. Migraine attacks can be triggered by specific foods or visual cues, but more commonly they occur without an apparent cause. Anti-migraine medications, two pieces of evidence implicate 5-Hydroxy Tryptamine (5-HT) in the development of migraines. The first is a sharp increase in the excretion of the main 5-HT metabolite, 5-Hydroxy Indole Acetic Acid (5-HIAA), during an attack, which decreases platelet 5-HT. The second

is that many drugs effective in treating migraines are either 5-HT receptor agonists or antagonists.

FORMULATION INGREDIENTS

1. Active pharmaceutical ingredient
2. Film forming agent
3. Plasticizer
4. Saliva simulating agent
5. Sweetening agent
6. Colouring agent
7. Flavouring agent

Active pharmaceutical ingredients

The technology of fast dissolving oral films is utilized for administering active pharmaceutical ingredients (APIs). It is simple to include low-dose molecules into the films, with up to 50mg being possible to include in a thin film. Incorporating high molecular weight molecules into an oral strip is challenging, and it limits the size of the dosage form. A typical film composition comprises 1-30%w/w of the drug. The texture of the film can be enhanced by using micronized API, resulting in improved dissolution and uniform distribution of the drug within the film14.

Film forming polymers

Film formers are utilized as agents in the production of FDFs, serving as their base and contributing to rapid disintegration and mechanical properties. They also enhance the mouthfeel of the FDFs. Increasing the molecular weight of the polymer film base reduces the disintegration rate of the polymer. Commonly used polymers in FDFs include HPMC (Hydroxyl Propyl Methyl Cellulose) E15, E3, sodium carboxyl methyl cellulose, polyvinyl pyrolidone, and polyethylene glycol 400.

Plasticizer

The FDF's rely on these plasticizers to enhance their mechanical properties. These plasticizers primarily improve the percentage elongation and tensile strength of the FDF's. Utilizing an optimized quantity of plasticizers is essential for achieving superior FDF's. Commonly employed plasticizers include Polyethylene Glycol (400, 4000, etc.) and glycerol.

Saliva stimulating agents

The purpose of these is to enhance saliva production, which aids in the rapid breakdown of fast-dissolving strip formulations. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are examples of salivary stimulants. Citric acid is the most favoured among these options.

Sweetening agents

Sweetening agents play a crucial role in oral pharmaceutical products by helping to mask the bitter taste of drugs. Various sweetening agents, including sucrose, dextrose, fructose, and glucose, are used in the formulation of FDFs. Polyhydric alcohols like sorbitol and mannitol are also utilized, often in combination, to reduce carcinogenic activity and act as cooling agents.

Colouring agents

The film formation has colouring agents added to it in order to give colour to the FDFs. The colouring agents need to work well with the drug and other components.

Flavours

Flavours are incorporated to enhance the taste of the film. Different flavours are used in the film production. Any flavour such as strong mint, tangy fruit, or sweet confectionary flavours can be included in the fast-dissolving film formulation. The optimal amount of flavour was integrated into the fast-dissolving films. These flavouring agents must be compatible with the medication and other components. The selection of flavours varies based on factors such as age; for example, elderly patients prefer mint or orange flavours, while younger individuals prefer fruity flavours15.

HYDROPHILIC POLYMERS

Buccal films utilize hydrophilic polymers as film formers to produce rapidly dissolving films that promptly release medication into the body upon contact with fluid. These polymers aid in the

hydration and dissolution of the film when applied to the oral mucosa, guaranteeing absorption of the medication. Furthermore, hydrophilic polymers can enhance the mouth feel and mechanical characteristics of the film.

Hydroxypropyl methyl cellulose (HPMC) E15

HPMC, also known as hydroxypropyl methylcellulose or hypromellose, is a type of soluble methylcellulose ether. It serves as a thickening agent, binder, film former, and hydrophilic matrix material. There are different viscosity grades of HPMC polymers used for creating hydrophilic matrix systems.

Hydroxypropyl methyl cellulose (HPMC) E3

The solubility and thermo-plasticity properties of HPMC are distinct, along with a diverse range of viscosity grades. Flexible and transparent films can be formed from its solution. The solutions remain stable within a pH range of 3–11 and experience a reversible sol-gel transformation, with gelation occurring at temperatures between 50–90 °c.

Advantages of HPMC

The benefits of HPMC include its excellent acceptability and good film-forming properties. In aqueous solutions, HPMC creates tough, flexible, and transparent films.

Polyvinyl pyrolidone

PVP, also known as polyvinylpyrrolidone, is a film-forming polymer that is commonly utilized in pharmaceutical technology for creating buccal films. Its characteristics include non-ionic nature, film-forming ability, adhesiveness, and affinity for interacting with hydrophilic substances such as gelatine. Furthermore, PVP is recognized for being inert, non-toxic, and having high swelling properties. When combined with other hydrophilic polymers, PVP can enhance the mechanical, mucoadhesive, and film-forming properties of the film16.

The advantages of PVP

It easily soluble in water and most other solvents. PVP also possesses a high capacity for forming films. Additionally, it can form water-soluble complexes with insoluble APIs, enhancing their release rate and solubility. PVP is non-toxic and chemically inert. Moreover, it is resistant to temperature, stable in pH, and colourless. Films made from PVP are clear, glossy, and hard.

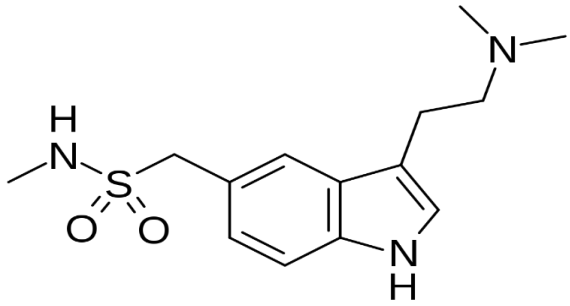
Polyethylene glycol 400

Polyethylene glycol 400, also known as PEG-400, functions as a plasticizer in buccal films, which offer a viable option to traditional pills for administering medication. When placed on the tongue or inside the cheek, buccal films dissolve rapidly to disperse the active ingredient. This approach is suitable for administering drugs that have an impact on the mucosa, either locally or systemically.

Sodium carboxyl methyl cellulose

CMC has the potential to function as a flocculating agent, chelating agent, emulsifier, thickening agent, water-retaining agent, sizing agent, and film-forming material, and more.

Sumatriptan succinate



Sumatriptan effectively ends or reduces the severity of migraine and cluster headaches. Its effectiveness is highest when it is taken soon after the pain begins. Injected sumatriptan is superior to other forms in terms of effectiveness. Sumatriptan's molecular structure is similar to that of serotonin (5-HT), and it functions as an agonist for 5-HT receptors (specifically type's 5-HT1D and 5-HT). The main therapeutic effect of sumatriptan is attributed to its ability to inhibit the release of Calcitonin gene-related peptide

(CGRP), likely through its action as an agonist for the 5-HT1D/1B receptors. The effectiveness of newly developed CGRP-targeting drugs and antibodies for the preventive treatment of migraines provides evidence supporting this. The exact mechanism by which agonism of the 5-HT1D/1B receptors inhibits CGRP release is not completely understood. It is believed that CGRP contributes to the pain experienced in migraines by causing sensitization of trigeminal nociceptive neurons17.

Pharmacokinetics

Several forms are available for administering Sumatriptan: tablets, subcutaneous injection, and nasal spray. The bioavailability of the oral administration (as succinate salt) is low, partly because of presystemic metabolism, leading to some breakdown in the stomach and bloodstream before reaching the target arteries. A rapid-release tablet formulation with similar bioavailability but a higher concentration can produce therapeutic effects on average 10–15 minutes earlier than other oral formulations. When sumatriptan is administered via injection, it typically takes effect within 10 minutes, but the duration of the effect is shorter. The primary metabolic pathway of sumatriptan involves monoamine oxidase A, which converts it into 2-{5-[(methylsulfamoyl) methyl]-indole-3-yl} acetic acid. Subsequently, this compound is conjugated to glucuronic acid and excreted in the urine and bile. Only a small percentage, around 3%, of the active drug is excreted unchanged18.

OTHER TECHNOLOGIES USED IN THE FORMULATION OF FAST DISSOLVING ORAL FILMS

Foamburst

This technology has been modified to include the introduction of an inert gas into the film during production. As a result, the film develops a honeycombed structure and dissolves quickly, creating a unique sensation in the mouth.

Xgel

The XGEL film systems have the capability to encapsulate any oral dosage form and can dissolve in cold or hot water. XGEL™ film consists of various water-soluble polymers, which have been tailored for their specific purpose. All the ingredients in XGELTM are widely recognized and considered safe (GRAS).

Wafer Tab

The taste of the Wafer Tab filmstrip can be enhanced by adding flavour to effectively mask any unpleasant taste. The active pharmaceutical ingredient (API) is accurately measured and incorporated into the body of a pre-manufactured XGEL film, reducing exposure to unnecessary heat and moisture, potentially improving the stability of the product. The Wafer Tab technology enables the joining of several films with distinct active ingredients, providing a variety of alternatives for innovative product design. Wafer Tab can be shaped and sized in various ways and is an excellent method for administering medications that need rapid release or for patients who struggle with swallowing19.

PACKAGING

Manufacturing and storage of fast dissolving dosage forms require expensive packaging, specific processing, and special care to ensure protection. It is necessary to use single packaging, and the most commonly used material for this purpose is an aluminium pouch. APR-Lab tec has created the Rapid card, a unique and patented packaging system specifically designed for Rapid films. This innovative system, with the same size as a credit card, can hold three films on each side and allows for individual removal of each dose.

The chosen material should possess the following qualities:

1. It should not react with the product.
2. It should shield the product from environmental factors.
3. It must have FDA approval.

4. It should be resistant to tampering.
5. It must be non-hazardous.

Packaging materials Foil, paper or plastic pouches

The flexible pouch offers ample tamper resistance and strong environmental protection. It is created during product filling using vertical or horizontal forming, filling, or sealing equipment. These pouches can be either single or aluminium pouches. The Fast dissolving oral thin film drug delivery pouch is a peelable pouch designed for fast dissolving soluble films with high barrier properties, and it allows for product visibility due to its transparent nature. Utilizing a two structure combination enables one side to be clear while the other utilizes cost-effective foil lamination. The foil lamination effectively blocks the transmission of both gas and moisture. This single dose pouch ensures both product and dosage protection20, 29. The blister card contains multiple units.

a) The blister, which is the shaped cavity that contains the product

b) The lid stock, which seals the blister

The blister package is created by softening a sheet of thermoplastic resin using heat and then using vacuum to draw the softened sheet of plastic into a molded shape. Once the plastic has cooled, it is removed from the mold and moved to the filling station of the packaging machine. The previously formed partially rigid blister is then filled with the product and covered with a heat-sealable backing material, typically made of aluminium foil. The material used to make the cavity is plastic, which can be customized to protect the dosage form from moisture.

Barrier Films

There is a need for high barrier films for drug preparations due to their extreme sensitivity to moisture. Moisture protection can be provided using various materials like polychlorotrifluoroethylene film and polypropylene. Polypropylene exhibits excellent resistance to stress cracking under all conditions and serves as an effective barrier to gas and vapour, but it lacks clarity21.

EVALUATION OF ORAL FILMS

Morphology studies (Appearance)

Surface morphology is examined through the use of Scanning Electron Microscopy (SEM). Pore presence, evenness of the surface, and distribution of particles are observable.

Thickness measurements

Each film's thickness is measured at five different positions (center and four corners) utilizing Vernier calliper micrometre. The data is expressed as an average ± standard deviation of five repeated determinations analysis.

Weight variation

Five samples measuring one square centimetre each are cut to represent different regions. The weight of each film strip is measured, and the weight difference is then calculated.

Folding endurance

The film's folding endurance is determined through the repetitive folding of one film at the same location until it ruptures. The quantity of times the film can be folded at the same spot without breaking is recorded, thus determining the value of the folding endurance22.

Determination of moisture uptake

The films are shaped in a specific way. To determine the moisture absorption of the films, they are placed in an environment with specific relative humidity and temperature for one week. The amount of moisture absorbed by the films is then measured, and the percentage increase in weight is calculated using a formula.

% increase in weight= [(Final weight- Initial weight)/ Initial weight] x 100

Content uniformity

The API content in individual film is estimated spectrophotometrically by using 20 films for determining the content uniformity. The content uniformity must fall within the range of 85-115%,

and the relative standard deviation should not exceed 6%.

Tensile strength

The apparatus used to determine tensile strength consists of two clamps, with one fixed at the top and the other movable at the bottom. A film sample measuring 0.5×3 cm is secured between the two clamps, and the force required for tearing and elongation is measured23, 26.

The percent elongation (%E) is calculated using the following equation

% E = {(Ls-Lo) / Lo} x 100

Where, Lo = Original length Ls = Length of the film after elongation

The modulus of elasticity of films was calculated from the equation

F/A = EM {(Ls-Lo) / Lo}

Where F = Breaking load (N), A = Cross-sectional area of the film EM = Modulus of elasticity.

Surface pH of films

On an petri plate, films are allowed to expand for 2 hours after being created by mixing 2% w/v agar into a warmed isotonic solution with desired qualities, stirring the mixture, and then pouring it into a petri dish until it gels at room temperature. The pH of the surface can be determined by using pH paper positioned on top of the expanded film.

In vitro disintegration time

The disintegration time is visually determined in a glass beaker using 10 ml of distilled water, and the mixture is swirled every 10 seconds. It is the time when the film begins to break or disintegrate24, 27.

In Vitro dissolution study

The drug release experiments utilize the USP dissolution test apparatus using the Paddle method. The temperature of the USP dissolution apparatus is maintained at 37 ±1oC while being stirred at a rate of 50 revolutions per minute. A glass slide holds each film, which is then placed into a vessel containing 500 ml of phosphate buffer pH 6.8. One ml aliquots are withdrawn at time intervals of 2, 4, 6, 8, and 10 minutes and replaced with an equal amount of dissolution medium. Sink conditions are upheld for the entire duration of the study. The absorbance is measured using the chosen analytical method25, 28, 30.

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HOW TO CITE: Sandhra S.*, Roopesh P. T., Anagha Mohan, M.Roshni, Megha V. S., Haritha K., And Sindhu V., Sumatriptan Succinate Loaded Oral Films For Potential Treatment Of Migraine: In Vitro Study, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 2242-2255. https://doi.org/10.5281/zenodo.13137462