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STUDIES ON EFFECT OF DIFFERENT POLYMERS FOR THE PREPARATION OF FAST DISSOVING ORAL FILMS OF SUMATRIPTAN SUCCINATE

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ABSTRACT

Sumatriptan succinate is an effective medication for treating migraines. Due to its high first pass metabolism, its oral bioavailability is limited. The aim of the present research is to circumvent the first pass effect by utilizing the solvent casting process to create rapidly dissolving oral films containing sumatriptan succinate. A rapid onset of action and immediate relief of symptoms can be achieved through the use of fast dissolving films. Therefore, fast dissolving films are the preferred formulations as they are soluble in saliva, releasing the drug within 6 minutes. The bioavailability of the drug in film dosage form is higher than in conventional dosage forms. Fast dissolving oral films reduce the lag time, resulting in a quicker onset of action. Oral films disintegrate rapidly in the mouth, allowing most of the medication to enter the systemic circulation through the buccal/oral mucosa, bypassing first-pass metabolism. Polymers such as HPMC E3 and E15 are used as film formers, while Sodium CMC, Polyvinyl pyrrolidone, and PEG 4000 are used as plasticizers to prepare the oral films, which were then evaluated for mechanical properties, disintegration, and in vitro dissolution. Fast dissolving oral films provide an appealing option for systemic drug delivery. The oral mucosa is an attractive and practical site for systemic drug delivery due to its increased systemic bioavailability, better permeability, and large surface area of absorption, ease of ingestion and swallowing, and pain avoidance. Rapidly dissolving dosage forms are also known as quick dissolving delivery systems, quick disintegrating, oral dissolve dosage forms, or melt-in-mouth dosage forms. It was observed that the concentrations of plasticizer and polymer had an impact on the properties of the strips. Dissolution studies were conducted in distilled water for 15 minutes, and all the formulations exhibited the release of more than 50% of the drug within the first 6 minutes, highlighting the usefulness of fast dissolving oral films for drug delivery. The prepared films were assessed for uniformity of weight, thickness, folding endurance, surface pH, drug content, tensile strength, percentage of moisture content, and in vitro dissolution studies.

KEYWORDS: Sumatriptan succinate, Fast dissolving film, polymer, Anti migraine, Oral film.

INTRODUCTION

A chronic neurological illness called migraine is typified by excruciating headache attacks that are frequently accompanied by additional autonomic nervous system symptoms such nausea, vomiting, photophobia, and phono phobia.[1] The primary cause of migraine episodes is changes in the activity of 5-hydroxytryptamine (5-HT)-containing neurons, which cause the trigeminal system to depolarize and produce neuropeptides that are vasoactive. The most often prescribed family of medications for treating migraines are triptans, which are serotonin 5-HT1B/1D receptor agonists.[2] They work by narrowing the cranial blood arteries and preventing the production of vasoactive neuropeptides. In order to alleviate the swallowing issues and choking anxiety associated with traditional solid orals, notably for paediatric, elderly, and bedridden patients, Films were originally created in the late 1970s.[3] Oral drug delivery is a popular and practical method of giving medication. It comes in a variety of forms, including tablets, capsules, liquids, powders, chewable tablets, effervescent tablets, controlled-release formulations, buccal and sublingual administration, gastrointestinal coatings, sustained-release, and extended-release formulations.[4] With the benefits and considerations that are specific to each approach, there is flexibility in meeting the needs of patients. Oral medication delivery is attractive because it is affordable, easy to administer, and patient-complies.[5] However, a number of variables, including the drug's features, the patient's health, and the way food interacts with the digestive system, affect how effective these techniques.[6] When choosing the best oral drug delivery technique for a particular prescription and patient, medical professionals carefully consider these aspects to provide the best possible therapeutic results. For several convincing reasons, oral fast-dissolving films have become more significant in modern pharmacological research. Films are excellent at improving patient

compliance because of their easy-to-use composition, quick disintegration, and delicious taste especially in groups like youngsters and the elderly.[7] This encourages adherence to recommended therapies, which improves treatment results. Moreover, films address the unique challenges posed by paediatric and geriatric patients who often struggle with swallowing difficulties, offering an effective and convenient medication administration solution.[8] Films also hold promise in improving drug bioavailability by enabling direct absorption through the oral mucosa, circumventing first-pass hepatic metabolism.[9] In contrast to conventional oral dose forms, this may lead to a quicker start of action and more effective drug delivery[10] According to the manufacturer, mucoadhesive preparations "may be supplied as buccal tablets, mucoadhesive films, or other mucoadhesive solid or semisolid preparations," and their purpose is to remain in the oral cavity.[11] The European Pharmacopoeia states that adherence to the mucosal epithelium and the potential to alter systemic medication absorption at the site of application.[12] Due to their flexibility, fast-dissolving films represent the most advanced and contemporary kind of solid dosage form. When compared to dissolving tablets, it enhances the effectiveness of the active pharmaceutical ingredient (API) dissolving in the oral cavity in a short length of time when exposed to less saliva.[13] When fast dissolving film is manufactured, a hydrophilic polymer is used, which dissolves fast over the tongue or buccal mucosa and delivers the medication to the bloodstream through the mucosa.[14] The rapid medication delivery method is specifically made to go through a low dosage and significant presystolic metabolism. With the purpose of improving bioavailability.[15]

1.2 Advantages[16]

1. Bioavailability: Site-specific targeting and increased drug bioavailability are provided by oral fast-dissolving films, which boost therapeutic effectiveness.
2. Passive Drug Diffusion: Two penetration paths are used by these films: passive drug diffusion across the oral mucosa and route Para cellular.
3. Patient Compliance and Convenience: FDFs are patient-friendly since they are non-invasive and easy to use.
4. Non-Invasiveness: Because FDFs don't require any incisions, they are a better option than other oral dose forms.
5. Site-Specific Drug administration: OFDFs enable the administration of drugs to specific oral sites, enhancing the medication's therapeutic impact.
6. Sturdy and Fragile: OFDFs are not as sturdy as conventional tablets and capsules, yet they.
7. Overcoming Resistance: Drug resistance may be overcome by using OFDFs, which are made to release medication toward the rear of the mouth.
8. Getting Past Physical Obstacles: OFDFs may be made to release medication toward the rear of the mouth, which can aid in getting past physical obstacles are still intact until they get to the stomach.

1.3 Disadvantages

1. Limitation of dose (1–30 mg).
2. Achieving dose consistency can be difficult.
3. Hygroscopicity (avoid contact with dampness).
4. This method can only be used to give medications that are absorbed by passive diffusion.
5. Special packaging needed to ensure the stability and safety of the product.
6. Problems with drug/polymer stability due to thermal processing.
7. The polymer's flow characteristics are crucial for processing.

1.4 MIGRAINE[17,18, 19]

Sensory afferents from the meningeal arteries (depicted as yellow lines) travel through the trigeminal ganglion and connect with the trigeminocervical complex (TCC) second-order neurons17. These neurons ascend through the Quinto thalamic tract after crossing in the brainstem, and they form connections with neurons in the thalamus. From there, they transmit ascending signals to the cortex (shown as blue lines). The reflex link between the superior salivatory nucleus and the parasympathetic output to the cranial vasculature is mediated by the pterygopalatine ganglion (depicted as pink lines). The activation of these pathways leads to vasodilatation due to the release of various neurotransmitters (labelled as insert A). The trigeminal nerve ending is thought to be influenced by neurotransmitters such as calcitonin gene-related peptide, substance, neurokinin, and pituitary adenylate cyclase-activating peptide (depicted as insert B). On the other hand, acetylcholine, vasoactive intestinal peptide, nitrous oxide, and neuropeptide Y (NPY) (labelled as insert C) are the suspected neurotransmitters involved at parasympathetic nerve ends. The rostral ventromedial medulla, periaqueductal grey, hypothalamus, and A11 nucleus (depicted as red lines) are responsible for regulating the descending trigeminovascular nociceptive inputs. Additionally, there are additional ascending connections (depicted as blue dotted lines) between the trigeminocervical complex and the locus coeruleus, and the cortex indirectly. The duration and clinical condition of migraines, as well as the associated triggers and symptoms, are defined by modulatory systems. Triptans act as agonists at 5-hydroxytryptamine (5-HT) 1B/1D/IF receptors and mimic serotonin. They are located centrally at the TCC on pre- and postsynaptic sites (labelled as insert D), reducing the flow of nociceptive traffic. In the periphery, they are situated on prejunctional nerve terminals that innervate dural arterial blood vessels (labelled as insert B). Via 5-HT1D receptors, they primarily inhibit the production, and through 5-HT1B receptors, they induce vasoconstriction in the arteries themselves.

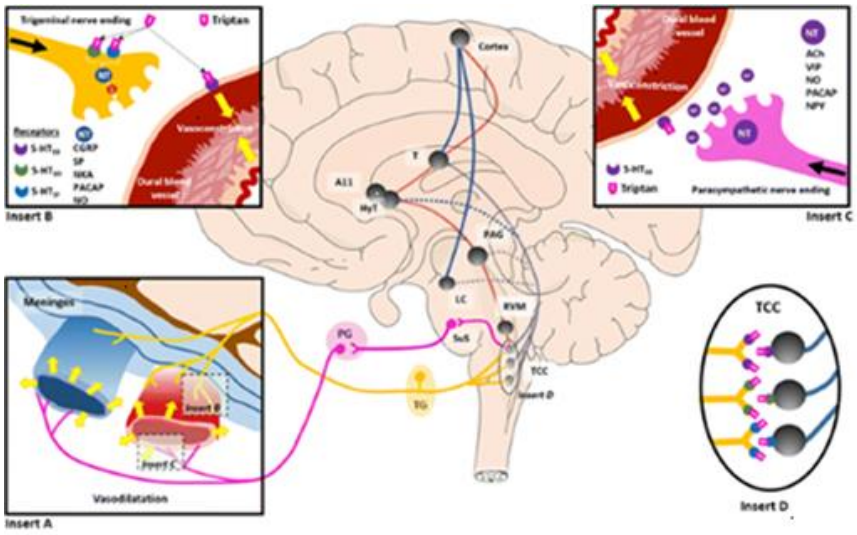

Figure No. 1 Pre and post receptor channel transmitter.

1.5 ANTI MIGRAINE DRUG[20,21,22]

Sumatriptan was the first medication in this group to be created, synthesized by Patrick Humphrey and his team in the UK. Their goal was to develop a medication with ergot-like properties but without the negative effects of vasoconstriction. The hypothesis in the 1960s was that vasoconstriction caused by ergotamine, noradrenaline, and 5-HT reduced the frequency of migraine episodes. This led to the global marketing of sumatriptan by 1991. Injectable subcutaneous sumatriptan, among the triptan class, was the first to be widely available. These medications are derivatives of the intercellular signal molecule indole and belong to the tryptamine family with modifications in positions 3 and 5. The side chains on the indole ring vary among the different triptans, and the structure of indole is similar to that of 5-HT. The primary differences lie in the presence of a nitrogen-alkyl chain in position 3 and a sulphonamide moiety in position 5 linked to a different side chain. Eletriptan's chemical structure replaces the nitrogen-alkyl chain linked to the indole ring with a dimethylpyrrolidine ring, while naratriptan replaces it with a 1-methylpiperidine ring.

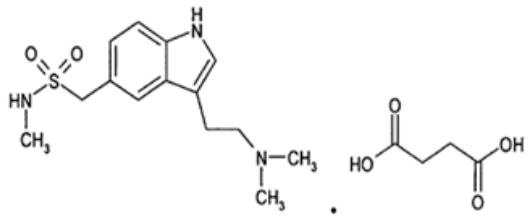

Figure No. 2: Structure of Sumatriptan Succinate.

For the Fischer indole synthesis, the required hydrazine derivative was prepared by hydrogenating N-methyl-4-nitrobenzenemethanesulfonamide. Following this step, diazotation and reduction of the diazonium salt were carried out using tin chloride in the synthesis of Glaxo's sumatriptan. The hydrazone resulting from the condensation of 4, 4-dimethoxy-N, N-dimethylbutylamine was then utilized in the Fischer indole synthesis with the Lang held ester. The Lang held ester, an ethyl metaphosphate, was first synthesized in 1910 at the University of Breslau by Kurt Lang held using phosphorus pentoxide and diethyl ether. The low yield at the final stage is partly attributed to the production of side products A and B. Sumatriptan's structure consists of a 3, 5-dialkylindole with a nucleophilic centre at position 2 and an XCH2 group at position 5, where X can act as a leaving group under acid catalysis in standard Fischer indole processes. This property is shared by almotriptan and rizatriptan. The highly efficient and optimized synthesis of sumatriptan, developed by researchers at a former Boots site in Nottingham, UK, was the focus of a 1999 patent application. A single vessel is used for the diazotation, reduction, and hydrogenation of N-methyl-4-nitrobenzenemethanesulfonamide. Notably, the use of sodium dithionite instead of stannous chloride was a significant advancement, avoiding toxicological and environmental concerns. The hydrazine is condensed with 4-chlorobutanal dimethyl acetal in the Grandberg version of the Fischer indole synthesis, which is then rejected in the presence of disodium hydrogen phosphate. This leads to idolization and the displacement of the chloro group with the ammonia released during the formation of the indole ring. The synthesis of sumatriptan is completed by reductive amination using sodium borohydride and aqueous formaldehyde.

1.6 Overview of Oral Mucosa

Outermost layer of the oral cavity is composed of stratified epithelial cells, with an underlying basement membrane separating the outermost layer, the lamina propria, from the innermost layer, the submucosa. The tissue arrangement of the oral mucosa improves its permeability.[26]

The skin is less permeable to drugs compared to the oral mucosa, which makes it a less effective route of administration for drugs with poor skin absorption. The generation of oral epithelium is estimated to take 5-6 days. The thickness of the oral mucosa varies from place to place, with the oral mucosa being 500-800 µm thick. The composition of the epithelium varies depending on the location in the oral cavity. The epithelium is moderately impervious to water while non-keratinized epithelium does not have lipids they also contain small amounts of neutral lipids few polar lipids, like cholesterol and ceramides. The epithelia is found to be considerably greater permeable to water than keratinized epithelia.[27]

1.7 Oral cavity

The buccal epithelium produces mucus, which is made up of proteins and carbohydrates and is produced by 40-50 cell layers. Mucosa is 100-200 microns thick at the base of the mouth, tongue, and gums. Mucus, a small gelatinous fluid secreted by the submucosal layer, is composed of 90–99% water, 1–5% water-insoluble glycoproteins, and other components such as proteins, enzymes, electrolytes, and nucleic acids. The salivary glands secrete saliva and parotid saliva into the lobules, and the salivary duct is situated near the sublingual ducts and submandibular teeth.

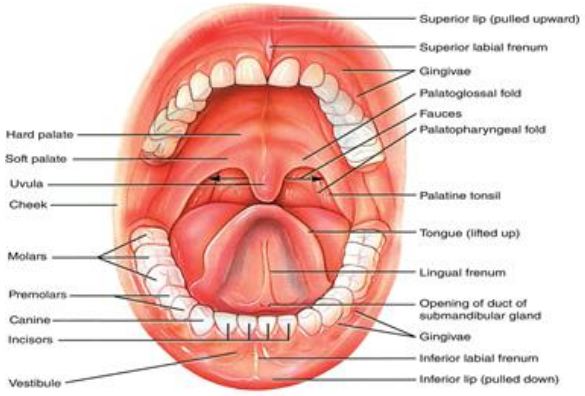

Figure No. 3: Oral Cavity.

The cheek and lip mucosa commonly contain small salivary glands. Saliva is produced in increments of about 1-2 ml per minute. It consists of mucus, water, lysozyme and amylase enzymes, mineral salts, immunoglobulins, and blood clotting factors. Saliva and mucus also act as protective barriers for the mouth mucosa. The mucosal epithelial structure can be divided into two regions: the more water-attracting area and the lipid-attracting gap between cells and the lipid-attracting membrane of the stratified epithelium. In terms of substance permeability, the oral mucosa is more resistant to substances than the intestinal mucosa and the epidermis. The permeability of the buccal mucosa is estimated to be 4–4000 times greater than that of the skin. The mucosal epithelium provides two main routes for medication absorption: the transcellular (intercellular) and Para cellular (intercellular) channels. Particles with high partition coefficients have an easier time getting through the lipophilic nature of cell membranes, whereas more polar hydrophilic molecules can penetrate the intercellular space. Whether a medicine is hydrophilic, hydrophobic, or amphiphilic affects how well it absorbs.[30]

1.8 Fast dissolving buccal film

A relatively new oral medicine delivery technology, offers immediate onset of action while protecting against stomach acidity and the first-pass impact because the oral breakdown and absorption processes take place there. It is an immediate-acting drug in a dry form.[31] For youngsters and elderly patients, films are the recommended medication administration method because to their ease of use over alternative methods. Fast dissolving films may be made in a ways. One such technique is solvent casting, which includes combining the polymer solution with the plasticizer and medication solution, stirring, taking out the air, putting the mixture to a dish, and heating it to remove the solvent. Solid dispersion, semisolid casting, and hot melt extrusion are further methods. The desired medication is rapidly dissolved by a spinning agent and mixed with the polymer solution to create quick dissolving forms.[32]

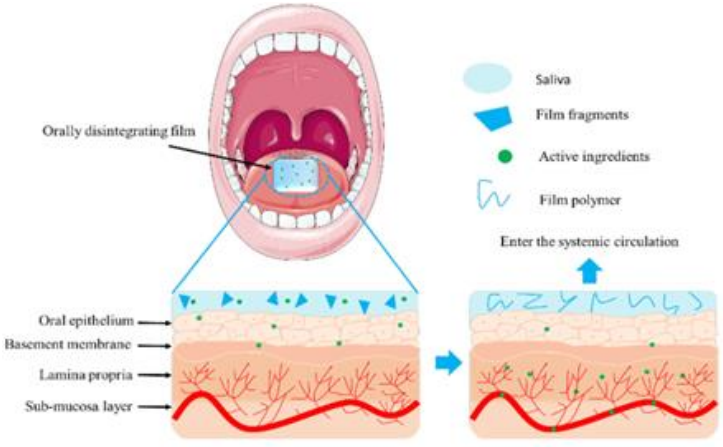

Figure No. 4: Fast Dissolving Buccal Film.

When the dosage form is put on the tongue or in the mouth, it may swiftly hydrate, attach, and dissolve to release the medication because word soluble polymers typically hydrocolloids, but sometimes bio adhesive polymers are used. They are also referred to as dispersible film, quick dissolving film, oral disintegrating film, and fast dissolving film. FDF can be a practical and effective delivery method for active substances that need to react with the human mucosa, including medications and breath freshness. The medication can be taken sublingually, orally, or intragastrically in order for it to enter the bloodstream.[33]

FDF facilitates quick sublingual absorption of the medication, which eventually leads to a quick start of therapeutic action. FDF must dissolve or disintegrate quickly in the buccal cavity, thus it's critical to formulate it with the correct excipients and ingredients. Depending on how it will be used, the formulation may also include other compounds including flavors, plasticizers, surfactants, colorants, sweeteners, saliva-stimulating agents, pharmacological agents, antibacterial agents, nutraceutical materials, and other excipients.[34]

1.9 Buccal epithelium

The buccal epithelium consists of a non-keratinized stratified squamous epithelium with multiple layers of cells exhibiting different maturation patterns from the surface to the deepest levels. Basal cells of the buccal epithelium can divide as cells progress towards the surface, maintaining a stable population of epithelial cells. Differentiation, followed by migration and desquamation of the surface cells, is necessary for tissue homeostasis.[35] Low molecular weight lipids and cytokeratin are accumulated by the prickle cells (intermediate layer), but they do not combine to create filaments. Membrane coating granules, also known as lamellar granules, are tiny organelles that contain an internal lipid component. These granules travel toward the cell's apical surface, where their lipid content is ejected into the extracellular space and their membrane merges with the cell membrane.[36]

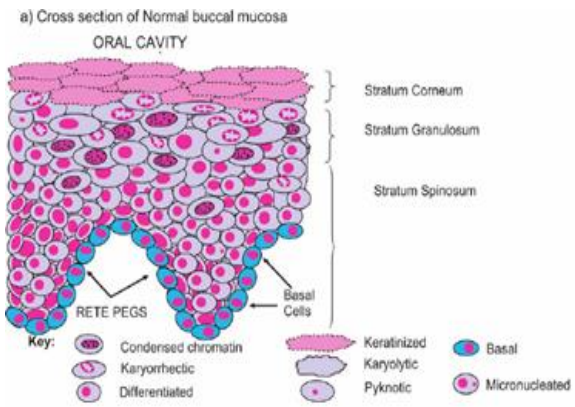

Figure No. 5: Oral Epithelium.

The buccal epithelium has weak intercellular connections called gap junctions, glydesmosomes, and hemi desmosomes but lacks tight junctions, which are present in the intestine and nasal mucosa. The basal epithelium, which acts as an uneven and continuous contact between the connective tissue and the epithelium, is upon which the epithelium rests. By strengthening the epithelium's barrier function and anchoring it to the connective tissue, the basal membrane keeps big molecules from penetrating the oral mucosa. Mouth fast-disposing tablets do not specifically aim to promote buccal absorption, although this is a possibility if the medication is discharged into the mouth cavity and comes into touch with the buccal mucosa. The buccal mucosa serves as the main route for transporting drugs, and there are two pathways for this process.

- Transcellular (intracellular)
- Para cellular (intercellular).[37]

1.10 SELECTION OF HYDROPHILIC POLYMERS[38]

One of the most important factors for the best possible film creation is the polymer selection. Both natural and synthetic polymers are used nowadays to create ODFs, however natural polymers are preferred because of their effectiveness, accessibility, and safety. Polymers used for ODF should ideally be non-toxic and non-irritating, non-bitter, tasteless, and free of leachable impurities. They should also have sufficient peel, shear, and tensile strength, a sufficient shelf life, and not be able to cause secondary infections in the oral cavity.

1.11 POLYMERS IN PREPARATION OF BUCCAL FILMS

These preparations contain a hydrophilic polymer that interacts with the mucus substrate to expand and adheres to the mucosal surface when moistened with saliva.

1.11.1 Mucoadhesive polymers

Mucoadhesive polymers ought to have certain properties that make interacting with mucins easier. First, polymers need to have the right amount of chain flexibility for the mucus's pH and ionic strength. An increase in chain flexibility is predicted to promote mucoadhesion and interpenetration within a homogenous class of polymers.[39]

1.11.2 Hydrophilic polymers

To increase hydration and adherence to the buccal mucosa, it can be applied to buccal films.

Muco adhesively may be increased by hydrophilic polymers, which have the ability to pierce mucin molecules and produce a robust gel. But according to one study, ex vivo mucoadhesive strength was actually reduced when the hydrophilic polymer PVP K30's content was raised.

Drugs that are hydrophilic can be applied to buccal films

as a solid solution or as dissolved material. Buccal films can also be engineered to enhance medication release in a regulated fashion.[40]

1.11.3 Ideal properties of polymers[41]

1. Not harmful.
2. Not irritating.
3. Bland.
4. Pleasant mouthfeel.
5. It should be steady throughout time.
6. Shouldn't change the characteristics of the formulation's other excipients or the active medicinal component.
7. Low-cost.
8. The ability to spread and wetting should be present.
9. The film's disintegration time shouldn't be prolonged.
10. Should possess ideal tensile and peel strengths.

1.12 Hydroxypropyl methylcellulose (HPMC)[42,43]

One or more of the three hydroxyl groups found in the cellulose ring have been replaced for hydroxyl groups in cellulose ethers, including hydroxypropyl methylcellulose (HPMC). Hydrophilic (water soluble), biodegradable, and biocompatible, HPMC is a polymer with several uses in medicine delivery, cosmetics, adhesives, coatings, dyes & paints, textiles, and agriculture.

It is also feasible to employ both aqueous and non-aqueous solvents with HPMC since it is soluble in polar organic solvents. Its solubility in both hot and cold organic solvents gives it remarkable features. When compared to other methyl cellulose substitutes, HPMC has higher thermo-plasticity and organo-solubility. When heated to a gelation temperature of 75–90°C, it gels.

1.12.1 Advantages of HPMC[44]

a) It has good film forming properties and excellent acceptability

b) In aqueous solutions, HPMC creates transparent, durable, and pliable films.

1.13 Sodium carboxymethyl cellulose (SCMC)[45]

This adhesive is made from cellulose, dissolves in water, and can be easily removed from fabric during finishing. It is available in various viscosities, offers strong film formation, and has significant adhesive properties. When combined with PVA and modified starch, it can be used on spun viscose and acrylic fibres. SCMC creates a durable, transparent, and pliable film. It has a tendency to absorb and retain moisture, so its ability to bind water reduces the need for high humidity in the weaving area compared to other sizing agents. The viscosity of SCMC decreases when the temperature rises and increases when it drops in solution.

CMC has the potential to act as a flocculating agent, chelating agent, emulsifier, thickening agent, water-retaining agent, sizing agent, and film-forming material. It is extensively used in various industries including electronics, pesticides, leather, plastics, printing, ceramics, and the daily-use chemical industry.

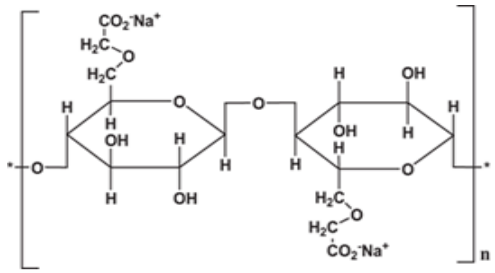

Figure No. 6: Structure of Sodium Cmc.

1.14 Polyethylene Glycol 4000[46]

Polyethylene glycol 400, also known as PEG 4000, is a type of low-molecular-weight Polyethylene glycol that exists as a clear, colourless, and viscous liquid. The number 400 in its name signifies the average molecular weight of the compound. Because of its low toxicity, Polyethylene glycol 4000 is extensively utilized in various pharmaceutical formulations. For instance, it aids in dissolving numerous substances that have limited solubility in water by creating complexes with active ingredients. This makes Polyethylene glycol 4000 an effective solubilizing agent for these active ingredients and excipients in both liquid and semi-solid preparations.

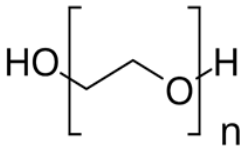

Figure No. 7: Structure PEG 4000.

Polyethylene glycol 4000 is utilized as viscosity modifiers and stabilizers in liquid pharmaceutical products and ointments. It is also an inactive ingredient in intravenous injections. It can dissolve in water, acetone, alcohols, benzene, glycerine, glycols, and aromatic hydrocarbons, and is somewhat soluble in aliphatic hydrocarbons. Low-molecular-weight formulations of Polyethylene glycol (e.g. PEG 4000) are employed in HP design jet printers to serve as a solvent for ink and lubricant for the print heads.

1.15 Poly vinyl pyrrolidone (PVP)

Polyvinylpyrrolidone (PVP), also known as polyvidone or povidone, is a polymer compound that dissolves in water and is produced from the monomer N-vinyl pyrrolidone. The PVP is available in different molecular weights and corresponding viscosities, allowing for selection based on the specific application properties desired.PVP or povidone is an amorphous, hygroscopic, synthetic polymer made up of linear 1-vinyl-2-pyrrolidinone groups. In the concentration range of 0.5%–5% w/w, PVP is used as a binder. Varying degrees of polymerization of PVP lead to polymers of different

molecular weights.[47]

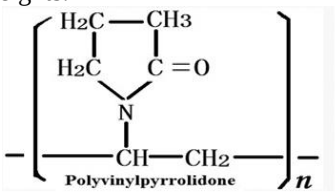

Figure No. 8: Structure of PVP.

The viscosity of povidone in aqueous solution is typically compared to that of water and indicated by a K value ranging from 10 to 120. Povidones with K values equal to or less than 30 are produced as spheres through spray drying, while those with higher K values are produced as plates through drum drying. Wet granulation using povidone K25/30/90 generally results in harder granules with improved flow characteristics compared to other binders, exhibiting lower friability and stronger binding. Additionally, povidone assists in enhancing the dissolution of APIs.

1.15.1 Advantages[48]

1) PVP readily dissolves in solvents.
2) PVP have high capacity for forming films.
3) PVP can form water-soluble complexes with insoluble APIs, enhancing their release rate and solubility.
4) PVP is non-toxic and chemically inert.
5) PVP is resistant to temperature, stable at various pH levels, and colourless.
6) The films produced are clear, glossy, and hard.

1.16 Composition of OFDFs[49]

The formulation of OFDFs is meticulously designed to achieve these properties while also ensuring the stability and effectiveness of (APIs). Typically, OFDFs contain the following crucial components.

Polymer Matrix: A water-soluble or water-dispersible polymer matrix serves as the primary structural element of OFDFs, forming the backbone of the film. Commonly used polymers include hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), polyvinyl alcohol (PVA), and pullulan. The required characteristics of the film, such as mechanical strength, disintegration rate, and API compatibility, dictate the choice of polymer.

Active Pharmaceutical Ingredient (API): The API, which the therapeutic agent intended to produce the desired pharmacological effect, is integrated into the OFDF formulation in a finely dispersed or molecularly dispersed form, ensuring even distribution within the film matrix.

Plasticizers are incorporated into the mixture to enhance the film's elasticity and flexibility, ensuring that it is easier for patients to handle and enabling proper film formation. Commonly used plasticizers include polyethylene glycol (PEG), glycerine, and sorbitol. Saliva stimulating agents are included to boost the production of saliva. Salivary stimulants typically consist of acids such as citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid. The agents are usually used in 2-6% w/w of the weight of the strip. Sweeteners are also employed as salivary stimulants. Sweeteners and flavouring agents are incorporated to enhance the palatability and patient acceptance of OFDFs. Sweeteners such as sucralose and mannitol, and flavouring agents such as mint and fruit flavours, can be added. These additives serve to disguise the taste of the API and offer a pleasant sensory experience during administration.

Pharmaceutical products for paediatric patients require sweeteners as an essential component. Two main types of sweeteners are commonly used: natural and artificial. While sucrose is the primary sweetener, dextrose, fructose, glucose, and malt also serve as sources of sweeteners. Diabetic patients have limited use of natural sugar, which is why artificial are commonly employed in pharmaceutical preparations. Surfactants can be added to facilitate the wetting of the film and its quick disintegration in the oral cavity, thereby enhancing the bioavailability of the active pharmaceutical ingredient (API). Antioxidants and preservatives are incorporated to safeguard the stability of the API and prevent degradation caused by exposure to light, oxygen, or moisture. Colorants are optional and are included for aesthetic purposes, allowing for differentiation between various formulations.

1.17 Role of polymers in film formation and disintegration[50]

The choice of polymer in the formulation significantly affects the disintegration and film formation processes of oral fast-dissolving films (OFDFs). Initially, polymers serve as the structural support for the film, maintaining its integrity and form while enclosing the active pharmaceutical ingredient (API) and other constituents. Flexible water-soluble or water-dispersible polymers such as hydroxypropylcellulose (HPC) and hydroxyl propyl methylcellulose (HPMC) provide the film with flexibility, enabling it to be handled and administered orally. These polymers also play a role in ensuring that the API is uniformly distributed within the film matrix, ensuring consistent dosing and therapeutic effectiveness. Furthermore, some polymers possess mucoadhesive properties that enable the film to stick to the oral mucosa. This enhances absorption and extends the duration of contact with the mucosal surface. In terms of disintegration, polymers readily absorb moisture from saliva upon contact, causing them to swell and disrupt the film matrix, thereby promoting rapid disintegration. Furthermore, polymers can improve the ability of the film to dissolve in saliva by spreading out and breaking down in the mouth, which helps in quickly releasing and dissolving the active pharmaceutical ingredient. Some polymers can even assist in taste masking by encasing the bitter or unpleasant taste of the API, thereby

improving patient acceptance during the disintegration process. Therefore, it is essential to select the appropriate polymers that possess ideal mechanical properties, water absorption, and disintegration traits in order to achieve the intended performance of OFDFs. This will guarantee the quick and consistent disintegration of OFDFs in the mouth, facilitating rapid release and absorption of the active pharmaceutical ingredient.

1.18 Impact of Plasticizer[51]

Plasticizers play a crucial role in enhancing the mechanical and flexible properties of polymer-based materials by increasing the mobility of polymer chains, improving elongation and tensile strength, boosting impact resistance, and reducing the modulus of elasticity. These qualities are particularly valuable in sectors such as packaging, automotive, construction, and textiles. However, it is important to carefully consider the potential effects of plasticizers on thermal stability and the environment, especially regarding health concerns associated with specific plasticizers like phthalates. As a result, there is an increasing focus on exploring environmentally friendly alternatives and emphasizing sustainable material development. A thorough understanding of how plasticizers influence material properties, as well as environmental and health considerations, is vital for responsible material design and application. This comprehensive overview highlights the multifaceted role of plasticizers in customizing polymer properties, which has relevance across a wide range of industrial sectors. In the context of Oral Fast Dissolving Films (OFDFs), addressing the solubility and compatibility of Active Pharmaceutical Ingredients (APIs) presents complex challenges and opportunities. API solubility, often hindered by poor water solubility, requires innovative approaches such as co-solvents, complexation techniques, and nanoparticle formulations to ensure uniform distribution within the film matrix. Ensuring compatibility between APIs and film materials is essential for preserving film integrity and bioavailability. This necessitates meticulous material selection and comprehensive compatibility studies. Furthermore, the solubility and compatibility of APIs significantly influence crucial film properties, including thickness, mechanical strength, flexibility, and disintegration time. Striking a delicate balance while accommodating the specific requirements of the API is crucial in the development of OFDFs. Researchers employ various strategies, including solid dispersion techniques and particle size reduction, to overcome these challenges. Regulatory compliance is essential, requiring rigorous demonstration of API solubility and compatibility, as well as stringent stability testing. Emerging technologies such as nanotechnology and hot melt extrusion provide innovative avenues to enhance API solubility and compatibility, potentially broadening the scope of available APIs for use in OFDFs.

1.20 Methods of preparation[52]

The following categorizes different techniques utilized to manufacture oral films.

Drying and casting:

(a) Semi-solid casting;

(b) Solvent casting.

Hot melt extrusion is one type of extrusion.

(a) Extrusion with solid dispersion

1.20.1 Solvent casting method[53,54]

Solvent casting is the most commonly used method for producing due to its low processing costs, easy application, and simple preparation process. In this technique, components that dissolve in water are combined in a heated magnetic stirrer to create a viscous solution. The medication and additional excipients are then added to this mixture to form the solution. Afterward, the solution is poured into a petri dish and allowed to evaporate the solvents for 20–25 hours at room temperature or for a shorter time at 40–50 °C in the oven, depending on the solvent system used. Once the solvents have evaporated, films of 15-20 mm diameter and 0.2–0.3 mm thickness are carefully removed from the petri dishes. These films are then cut into appropriately sized pieces based on the concentration of active ingredients they contain. In the solvent casting method, gel-forming polymers are used to dry the semisolid gel mass after pouring it into suitable molds. Following this, the films are cut into the appropriate sizes and are ready for use. This technique has been used in approximately 90% of cases for formulating films. One advantage of this method is that it produces films of uniform thickness and high flexibility. Additionally, the cost of this method is very low.

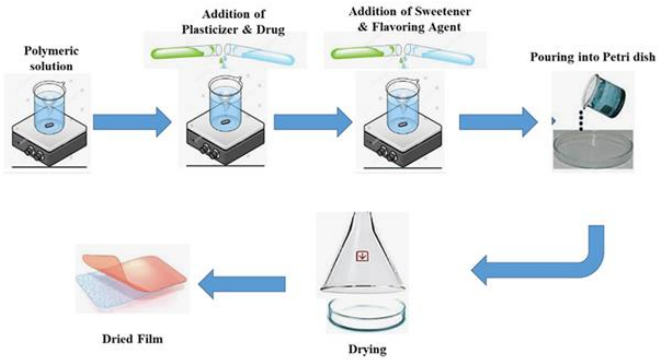

Figure No. 9: Solvent casting method.

The most traditional method of preparing FDFs is through solvent casting, a water-based process capable of handling both stable and unstable drugs by evaporating the solvent through heating. To prepare active pharmaceutical ingredients or plant extracts, the active substances are initially dissolved in distilled water or a volatile solvent that enables quick dissolution, followed by thorough mixing with a magnetic stirrer for consistency. The choice of solvents is based on the characteristics of the active substances, including compatibility with excipients and film forming polymers, as well as temperature sensitivity and polymorphic qualities. The film-forming polymer, colouring agent, plasticizer, and necessary excipients are individually prepared in distilled water, then the resulting solution, known as the film dope, is stirred for consistency. In a lab environment, the film dope is put to Petri plates, and after 24 hours, it is dried in a hot oven between 40 and 50 °C. Once thoroughly dried, the films are cut into the required sizes and stored in aluminium foil for analysis. In the case of impregnated paper, the film dope is applied and then transferred to a convection chamber to remove solvents. After drying, the films are sliced into small sections and individually wrapped in aluminium foil or stored in sealed pouches to protect against moisture, which can negatively impact stability and mechanical characteristics. It's crucial to control the temperature to preserve the viscosity of solutions. While the solvent casting method is suitable for heat- and light-sensitive active ingredients due to the lower temperatures required for volatile ingredients and solvent removal, it does have drawbacks, such as potential remnants of solvents that might impede adherence to quality standards. Additionally, precautions are necessary for volatile solvents like methanol and ethanol to prevent fires as they are flammable.

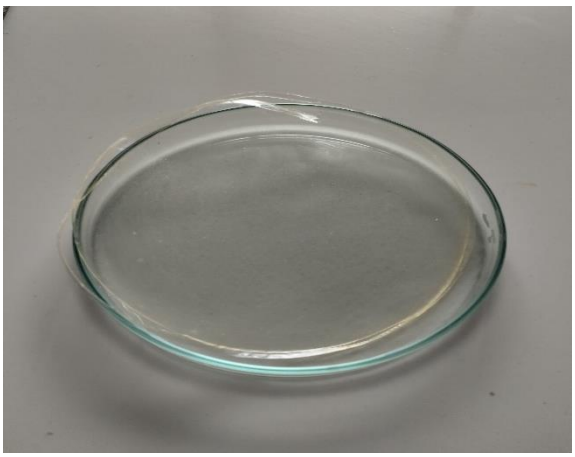

Figure No. 10: Casted film in a Petri plate.

Advantages[56]

a. When compared to extrusion, there is improved clarity and uniform thickness in the film.
b. The film has a glossy appearance and is free from imperfections such as die lines.
c. The film exhibits superior physical properties and increased flexibility.
d. While it is possible to achieve various thicknesses to accommodate API loading and dissolving needs, the suggested final film thickness typically ranges from 12 to 100 µm.

Disadvantages

1. The polymer must be soluble in water or a volatile solvent.
2. It must be feasible to create a stable solution with an appropriate minimum solid content and viscosity.
3. It needs to be possible to create a homogeneous film and for it to be detached from the casting support.

1.20.2 Hot-melt extrusion method[57]

Hot Melt Extrusion has been used to create transdermal delivery methods, sustained-release pills, and granules, drawing inspiration from the plastics manufacturing industry. Components for oral film manufacturing, such as combinations of drugs, polymers, and plasticizers, are extruded into different end forms to achieve the desired drug release profiles. This method is unique because of its use of heat treatment and absence of solvents.

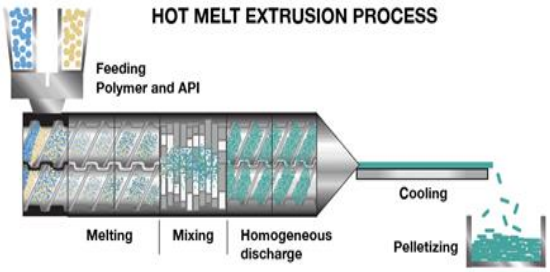

Figure No. 11: Hot melt extrusion.

Once the API and additional excipients are mixed in a dry state, the extruder's heaters apply heat to produce a molten mass that is extruded through the orifice. Once the films have cooled, they are cut to the required size. Hoffmann has explored the use of this method for continuous-release oral films, despite facing ongoing issues with film thickness and breakdown.[58] The HME procedure comes with certain limitations: it is most effective for heat-stable pharmaceuticals, and the search for heat-resistant film-forming polymers may pose a challenge.

1.20.2.1 Advantages

a. Solvent or water is not needed
b. The compressibility characteristics of the API may be insignificant
c. An excellent alternative for drugs with low solubility
d. Vigorous mixing and agitation lead to superior dispersion uniformity
e. It consumes less energy than high-shear methods.

1.20.2.2 Disadvantages

a. Exposure to elevated temperatures can lead to thermal degradation.
b. The flow properties of the polymer play a critical role

in processing.
c. Limited availability of polymers can be a drawback.
d. Excipients must not contain any water or volatile solvents.

1.20.3 Solid dispersion method[59]

The term solid dispersion refers to the scattering of one or more solid substances, like drugs or therapeutic agents, within another solid substance, such as an inert carrier like an amorphous hydrophilic polymer, using methods like hot melt extrusion (HME). In order to form a solution, the medication is initially dissolved in a suitable liquid solvent. Afterwards, this solution is blended into the molten polyol, for example polyethylene glycol, without removing the liquid solvent. There is a possibility that the medication or chosen solvent may not blend well with the molten polyethylene glycol. As it solidifies, a solid dispersion is created and the non-mixable components of the drug are pushed through dies to form the structure of the film. The polymorphic form of the drug that precipitates within the solid dispersion may vary depending on the type of liquid solvent used.

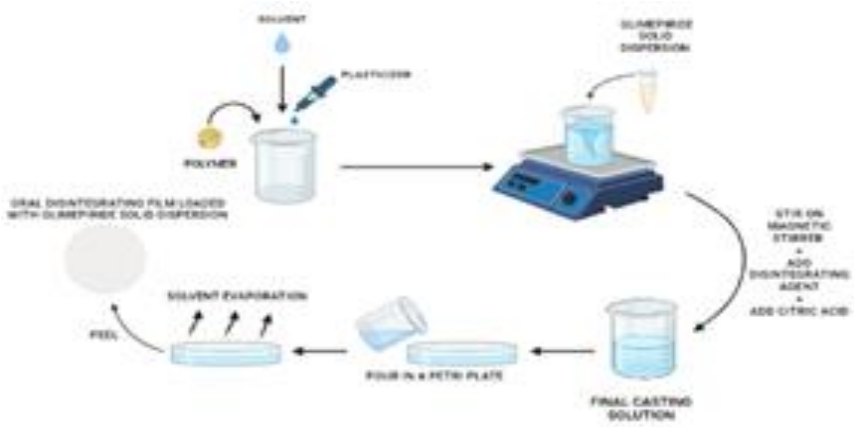

Figure No. 12 Solid dispersion method.

1.20.4 Rolling method[60,61]

During the rolling process, film formation begins with the preparation of the pre-mix, followed by the addition of the active ingredient and the subsequent formation of the film. The pre-mix batch, along with additional materials like polar solvent, film-forming polymer, and API, is introduced into the main batch feed tank. A predefined amount of the master batch is fed into the mixer by the first metering pump and control valve. Once the mixer contains the correct medication amount, it is mixed thoroughly to create a homogenized matrix. The second metering pump then feeds a specific amount of the matrix into the pan. The metering roller is used to measure the film thickness. Finally, the film is produced on the substrate and removed by the support roller. Controlled bottom drying is employed to dry the wet material.

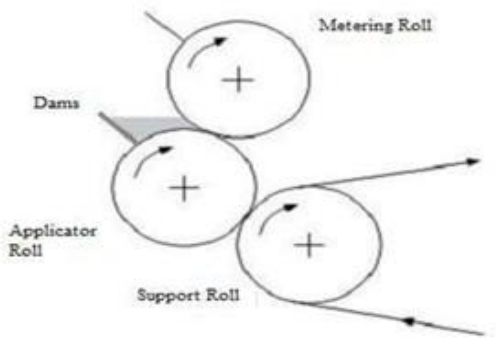

Figure No. 13: Rolling Method.

1.20.5 Semi Solid Casting Method[62,63]

When acid insoluble polymers such as cellulose acetate phthalate and cellulose acetate butyrate are utilized in the production of ODF, this approach is preferred. Initially, a solution of water-soluble polymers is prepared. This prepared solution is then combined with a solution of acid insoluble polymer. Then, using heat-controlled drums, the proper quantity of plasticizer is added to form a gel mass that will be cast into films. The film thickness measures approximately 0.015 – 0.05 inches. Acid insoluble polymer and film forming polymer are mixed in a 1:4 ratio.[64]

AIM

The aim of this study is to develop fast dissolving buccal film of sumatriptan succinate using different ratios on polymers for rapid release drug.

OBJECTIVES

- ❑ To formulate and evaluate oral fast dissolving films of sumatriptan succinate.
- ❑ To study the effect of various polymers and plasticizers in different concentrations on the release of sumatriptan succinate.
- ❑ To conduct preformulation studies for drug and excipients.
- ❑ To perform in-vitro evaluation studies
- Morphological properties.
- Weight determination.
- Thickness test.
- Tensile strength.

- Folding endurance.
- Percentage moisture absorption.
- Percentage moisture loss.
- Surface pH test
- Content uniformity
- In-vitro dissolution study
- Disintegration test
- Differential scanning calorimetry.
- Fourier transform infrared spectroscopy.
- Stability studies.
- Tack test.
- Entrapment efficiency.

❑ Selection of best Formulation of the fast-dissolving buccal film of sumatriptan succinate using different polymers in different ratios.

❑ To perform stability study for the optimized formulation.

❑ To perform kinetic data analysis of optimized formulation.

MATERIALS AND METHODS

Table No. 1: chemicals used for the preparations.

Sl.No	Materials / Solvents	Suppliers/Manufactures
1.	Sumatriptan succinate	Yarrow chem products, Mumbai.
2.	Hydroxyl propyl methyl cellulose E15	Kanton Laboratories, Kannur.
3.	Hydroxyl propyl methyl cellulose E3	Kanton Laboratories, Kannur.
4.	Sodium carboxyl methyl cellulose	Yarrow chem products, Mumbai.
5.	Polyvinylpyrollidone K30	Burgoyne Burbidge and Co.
6.	Polyethylene glycol 4000	Burgoyne Burbidge and Co.
7.	Distilled water	RIPSAR Trikaripur, Kasaragod. Kerala.

Equipment's used for the formulation and evaluations

Table No. 2: Equipment's used for the preparations.

Sl. No	Equipment	Suppliers/Manufactures
1.	Digital balance	Kerro Electronics
2.	Dissolution test apparatus	Electro lab
3.	Desiccator	Universal Agencies
4	FT-IR spectroscopy	FTIR-4600typeA
5.	Hot air oven	Rotek Instruments
6.	Magnetic stirrer	Rotek instruments
7.	pH meter	Roy Electronics
8.	Screw gauge	Universal Agencies
9.	Tensile strength	Fabricated
10.	UV-Spectrophotometer	Shimadzu

DRUG PROFILE[86]

Structure

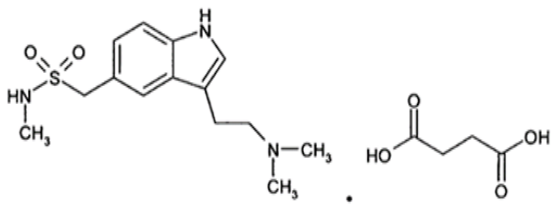

Figure No. 14: Structure of sumatriptan succinate.

Chemical name

Butanedioicacid; 1-[3-[2-(dimethylamine) ethyl]-1H-indol-5-yl]-N-methyl methane sulphonamide

Molecular formula: C18H27N3O6S

Description: After reacting sumatriptan with one equivalent of succinic acid, a succinate salt known as sumatriptan succinate is produced. Selective agonist, most likely from the 5-HT1D family, for a vascular 5-HT1 receptor subtype. Used to treat adults' severe migraines, whether or whether they have an aura. The compound functions as both a vasoconstrictor and a serotonergic agonist. A sumatriptan (1+) is present.

Molecular weight: 413.5 g/mol.

Melting point: Between 165°C and 169°C.

Storage: Store at room temperature.

Dosage: Three strengths of sumatriptan oral tablets are available:

25 milligrams (mg)

50 mg

100 mg

Solubility: DMSO 83 mg/mL (200.73 mm)

Water 83 mg/mL (200.73 mm)

Ethanol Insoluble

Pharmacokinetic properties

Absorption: Both oral and subcutaneous administration

of sumatriptan result in fast absorption. On the other hand, subcutaneous injection of sumatriptan results in about 100% bioavailability, whereas oral treatment only achieves 14% bioavailability.

Protein bound: In circulation, 14%–21% of sumatriptan is bound protein.

Metabolism: Monoamine oxidase A is metabolism of sumatriptan. The inactive forms of indole acetic acid and indole acetic acid glucuronide are the primary.
Metabolites: Ester Glucuronide of GR49336 (Sumatriptan Metabolite GR49336), GR34633 (Sumatriptan Metabolite).

Route of elimination: About 40% of drug is eliminated from the faces, whereas 38±7% drug eliminated from the urine as indole acetic acid and 22±4% as unaltered sumatriptan.

Half-life: The half-life of subcutaneous sumatriptan is 1.9 hours (95% CI: 1.7-2.0 hours).The half-life of oral sumatriptan is 1.7 hours (95% CI: 1.4-1.9 hours). The half-life of rectal sumatriptan is 1.8 hours (95% CI: 1.6-2.2 hours). The half-life of intranasal sumatriptan is 1.8 hours (95% CI: 1.7-2.0 hours).

Drug class: Selective serotonin receptor agonists.

Mechanism of action: 5-HT1B and 5-HT1D agonists include sumatriptan. This agonism prevents the production of pro-inflammatory neuropeptides and causes the cerebral blood vessels to contract. While sumatriptan improves blood flow velocity in the middle cerebral artery and internal carotid artery, it reduces blood flow in the carotid artery.

Contraindication[87]

- It is not recommended to administer sumatriptan orally, intranasal, or subcutaneously to those who have significant liver impairment.
- Patients who are using MAO-An inhibitors now or who stopped taking them within the last two weeks owing to contraindications should not take sumatriptan.
- Patients with ischemic heart disease, which includes disorders including coronary artery vasospasm, myocardial infarction, Prinzmetal angina, and angina pectoris, should not use sumatriptan. Additionally, individuals who are concurrently taking ergotamine and another 5-HT1 agonist should not take sumatriptan.
- Patients who suffer from basilar migraine or hemiplegic migraine should not use sumatriptan.
- Due to contraindications, those with Wolff-Parkinson-White syndrome and arrhythmias linked to other cardiac accessory conduction circuit diseases should not take sumatriptan. If a patient has a history of hypersensitivity to sumatriptan or any of its excipients, they should avoid using the medication as anaphylaxis has been documented in these situations. If a patient has already experienced sumatriptan hypersensitivity reactions, clinicians should proceed with caution when prescribing other triptans to them.

Drug interaction

1,2-Benzodiazepine	Combining sumatriptan with 1, 2-Benzodiazepines may enhance the likelihood or Intensity of CNS depression.
Abemaciclib	Abemaciclib may slow down the pace at which sumatriptan is excreted, Thereby raising the serum level.
Acarbose	Using Acarbose in conjunction with Sumatriptan can enhance Its therapeutic effectiveness.
Acebutolol	Acebutolol may have less antihypertensive effects when used with sumatriptan.

Side effects[88]

- Having symptoms of illness (vomiting or nausea).
- Feeling fatigued, lightheaded, or unstable on your feet.
- Face flushes crimson while feeling hot or cold.
- Following use of the nasal spray, irritation or burning in your throat or nose.
- Bleeding nosebleeds following nasal spray use.
- After using the nasal spray, a bad taste remains in your mouth.

POLYMER PROFILE[89]

Hydroxypropyl methylcellulose (HPMC)

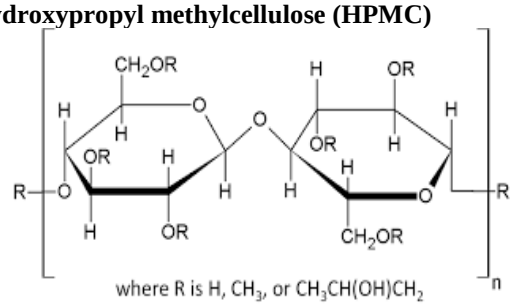

Figure No. 15: Structure of HPMC.

Synonyms: Cellulose, 2-hydroxypropyl methyl ether.
Molecular formula: C56H108O30
Chemical structure: R = H, $-CH_3$ or - $(OCH_2CHCH_3)_{xOH}$

Description: Polymeric compounds with hydroxypropyl methylcellulose repeating units in them. A hypromellose polymer's molecular weight, percentage of hydroxyl groups, percentage of hydroxypropyl groups, and viscosity measures are what determine its qualities, which can vary significantly. They are present in a wide range of commercial goods, including lubricants, excipients, and food additives.

Uses: Coatings with moderate strength, moderate moisture and oxygen barrier qualities, flexibility, transparency, and resistance to fat and oil are made utilizing HPMC as a basic material. Additionally, it may be utilized as a tablet matrix for longer release and as a tablet binder.

Sodium carboxymethyl cellulose (SCMC)[90]

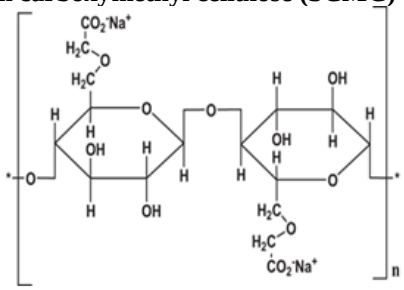

Figure No. 16: Structure of SCMC.

Synonyms: SODIUM CARBOXYMETHYL CELLULOSE,
Molecular formula: $C_8H_{15}NaO_8$
Chemical structure: CHO2 (OH) OCHCOONa] n
Description: Carboxymethylcellulose cellulose carboxymethyl ether is a hexose**.**
Uses: In detergents, SCMC is used as a stabilizer, homogenizer, skin protector, anti-soil redeposition agent, particle suspender, and texture protector.

Polyvinylpyrrolidone (PVP)[91]

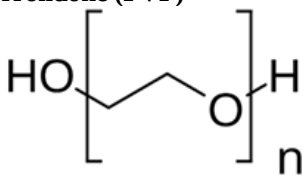

Figure No. 17: Structure of PVP.

Synonyms: polyvidone or povidone
Molecular formula: (C6H9NO) n
Chemical structure: (C6H9NO) n
Description: N-Vinyl-2-pyrrolidone is a member of pyrrolidin-2-ones**.**

Uses: When PVP and iodine are combined, a combination known as povidone-iodine is created that has antiseptic qualities. Several items, including ointments, surgical scrubs, pessaries, liquid soaps, and solutions, contain this complex. Pyodine and Betadine are commercial names for it.

Preparation of placebo film
Develop a placebo buccal film by following these procedures using HPMC E15, HPMC E3, PEG 4000, sodium carboxymethyl cellulose (SCMC), and PVP K30:
Materials Required:

1. Polymers for film formation: HPMC E3 and E15.
2. SCMC: To improve the qualities of films.
3. PEG 4000: Flexible plasticizer.
4. PVP K30: To increase the solubility and film adhesion.

Preparation Steps[92]

1. Polymer Solution Preparation: Weigh the Polymers: Utilize a ratio of PVP K30, SCMC, HPMCE15, HPMCE3.
   Dissolve HPMC E15 and E3: In a beaker, slowly heat and mix the chosen amounts of HPMC E15 and HPMC E3 in a specified volume of distilled water.
2. Add drug into the above mixture completely dissolved.
3. Add SCMC and PVP K30: To achieve equal dispersion, gradually add SCMC and PVP K30 to the HPMC solution while stirring constantly.
4. Incorporate PEG 4000: Incorporate PEG 4000 into the mixture as a plasticizer to increase its workability and flexibility. Mix well until well combined.
5. Casting film
6. Drying: Transfer the homogenous mixture on a petri dish, levelling it out
7. To the appropriate thickness. Let the dry at room temperature or in an oven set to a precise temperature (between 40 and 60 degrees Celsius) until the solvent has evaporated entirely
8. Film Removal: Carefully remove the film off the plate when it has dried.
9. Storage: To avoid moisture absorption, keep the placebo buccal films sealed in airtight containers in a cold, dry location.

Analysing the absorbance of sumatriptan succinate
UV-Vis spectroscopy is frequently used to analyse the absorbance of sumatriptan succinate, as it is a standard technique for figuring out how much of this molecule is in solution.
Make several standard solutions of sumatriptan succinate at known concentrations in the selected solvent.

Calibration Curve

- Calculate each standard solution's absorbance at the wavelength of 227 nm, which is the maximum absorbance of sumatriptan succinate.
- Draw an absorbance vs. concentration calibration

curve.

The amount of drug incorporated into polymeric mixtures

Area of petri plate=3.14×4.05^{2} = 51.5038

51.5038cm^2 area contain 51.5038mg of drug = 51.5038

= 51.5038×10

= 515.038 mg drug

4cm^2 = 10mg

Design of Experiment: 2^4 Factorial designs[93]

Thoroughly identifying the components and their amounts is necessary while designing a 24 factorial experiment for the formulation of fast-dissolving buccal films employing various polymer and excipient kinds. A suggested design utilizing sodium carboxymethyl cellulose (SCMC), polyethylene glycol (PEG 4000), polyvinylpyrrolidone (PVP K30), and hydroxypropyl methyl cellulose (HPMC) E15 and E3 is shown below.

Four factors, each with two levels (often recorded as -1 and +1), make up a full factorial experimental design known as a 2^4 factorial design.

Table No. 3: Factorial design for formulation and Formulation table of fast dissolving buccal film.

Run	A (HPMC E15)	B (HPMCE3)	C (PEG 4000)	D (PVP K 30)	E (SCMC)
1	-1	-1	-1	-1	-1
2	+1	-1	-1	-1	-1
3	-1	-1	-1	-1	+1
4	+1	-1	-1	-1	+1
5	-1	-1	+1	-1	-1
6	+1	-1	+1	-1	-1
7	-1	-1	+1	-1	+1
8	+1	-1	+1	-1	+1
9	+1	+1	+1	+1	-1
10	+1	-1	-1	+1	-1
11	-1	-1	+1	+1	+1
12	+1	-1	-1	+1	+1

Formulation code	HPMC E15	HPMC E3	SCMC	PEG 4000	PVP K 30	DRUG	Distilled water
F1	250 mg	150 mg	5 mg	10 mg	2 mg	10 mg	q.s
F2	400 mg	50 mg	5 mg	10 mg	2 mg	10 mg	q.s
F3	200 mg	150 mg	12 mg	10 mg	2 mg	10 mg	q.s
F4	400 mg	50 mg	12 mg	10 mg	2 mg	10 mg	q.s
F5	100 mg	150 mg	5 mg	30 mg	2 mg	10 mg	q.s
F6	400 mg	50 mg	5 mg	30 mg	2 mg	10 mg	q.s
F7	100 mg	250 mg	12 mg	30mg	2 mg	10 mg	q.s
F8	400 mg	50 mg	12 mg	30mg	2 mg	10 mg	q.s
F9	400 mg	150 mg	5 mg	20 mg	10mg	10 mg	q.s
F10	400 mg	50 mg	5 mg	10 mg	10mg	10mg	q.s
F11	200 mg	150 mg	12 mg	10 mg	10mg	10 mg	q.s
F12	400 mg	50 mg	12 mg	10 mg	10mg	10 mg	q.s

Morphological characteristics[94]

Fast dissolving buccal films' morphological characteristics are essential to assuring their durability, acceptance by patients, and effectiveness.

Film thickness[95]

Using a micrometre screw gauge, the thickness of the film was ascertained. Every film was measured five times (in the centre and four corners), and the average was computed. The formula for calculating the percentage reduction in film thickness was as follows:

Reduction in film thickness = (1 − film thickness dry/film thickness wet) x 10 times .The measurement was carried out.

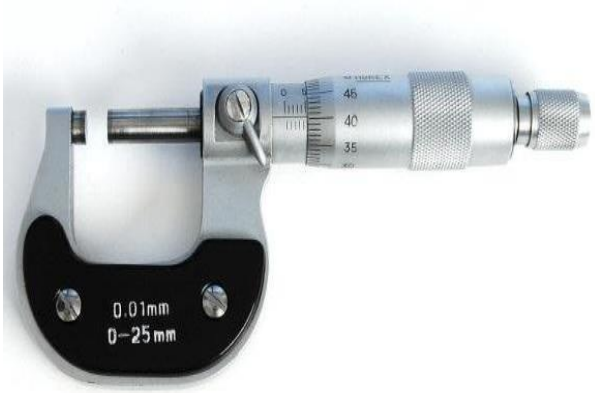

Figure no. 18: Screw gauge.

EVALUATIONS OF THE FILM

Content uniformity[96]

Typical response: Take 10 mg of sumatriptan succinate with 100 ml of 0.1NHCL to get ready. Take 1 ml of this and dilute it with 10 ml of 0.1 N HCL. At 227 nm, the absorbance is measured.

Test solution: From each formulation, three films are taken and dissolved in 100 millilitres of 0.1 NHCL. After filtering the solution, dilute it with HCL. At 227 nm, the absorbance is measured.

% Label claim = Abt/Abs × Ds/ Dt × 100/ Lc×100

Tensile strength[97]

It is defined as the highest stress a material experiences at the rupture point and is computed using the following formula: applied load at failure divided by the strip specimen's cross-sectional area.

1. **Prepare the film**: Cut the film into dumbbell-shaped strips and measure its thickness and width.
2. **Set up the texture analyser**: Position the two tensile grips of the texture analyser 30 mm apart.
3. **Test the film**: Place the film between the grips and gradually increase the force until the film breaks.
4. **Calculate the tensile strength**: Divide the force required to break the film by the film's cross-sectional area.
5. **Repeat the test**: Repeat the test three times and calculate the standard deviation.

Figure No.19 Tensile strength apparatus.

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-sectional area of film (cm2)}}$$

Folding endurance[98]

The number of folds necessary for breaking serves as a measure of a material, which is ascertained by folding it repeatedly in the same spot until it fractures.

Percentage moisture absorption[99]

Three films were measured precisely, weighed, and then put in a desiccator. The film was taken out after 72 hours, weighed, and the results were computed using a formula.

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}$$

Percentage moisture loss

Three 2 cm films were measured, and the precise weights were stored in desiccators. Film was removed and weighed after 72 hours. The computed moisture loss percentage were:

$$\frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial weight}}$$

Surface pH test

Oral film is dissolved in 10 millilitres of distilled water, and the pH of the resulting solution is measured to determine the pH value.

In vitro Disintegration time[100]

Three films from each formulation were collected and put in a Petri dish with a surface area of 6.3 cm2 and a wall height of 1.3 cm, which held a buffer solution with a pH of 6.8 to test for disintegration. When the image started to break is outlined. We calculated the standard deviation and mean.

In vitro dissolution studies[101]

Films of certain formulations were subjected to a 3-minute in vitro dissolving experiment using a pH 6.8 phosphate buffer solution. The dissolution medium was kept at 50 rpm and 37 0.5°C. The samples (5 mL) are taken out and replaced with fresh pH 6.8 phosphate buffer solution every 30 seconds. Next, a volumetric flask was used to dilute 10 mL of the 5 mL samples. The drug concentration of the samples was determined using an Electro Lab Ltd dissolving apparatus (U.V. spectrophotometer, maximum wavelength set at 256 nm). A significantly increased surface area of the medication for dissolution is the cause of an increased dissolution rate.

Drug content and % moisture content[102]

The films were dissolved in 100 ml of phosphate buffer (pH 6.8), appropriately diluted, and subjected to an analysis at 293 nm using a UV-Visible spectrophotometer in order to assess the homogeneity of drug content. Using a standard calibration curve and the mean of three measurements, the drug content was calculated. Because moisture in the film can have a significant impact on its mechanical strength, adhesive qualities, and friability, the percentage moisture content for each batch was calculated in triplicate.

Stability test

Stability studies must be carried out in the humidity chamber at accelerated temperatures (35 ºC and 65% relative humidity).

Drug release kinetics[103]

The main emphasis of kinetic studies for quickly dissolving buccal films is the drug release profile and the absorption kinetics of the medication from the film. To analyse the drug release mechanism and forecast the drug's in vivo properties, a variety of kinetic models are employed. The main kinematic elements of analysing

quickly disintegrating buccal films are listed below.

To ascertain the rate and volume of medication release over time, buccal film drug release is assessed. To match the drug release data and determine the release process, many kinetic models are used.

A. First order

A drug release mechanism where the rate of release is exactly proportional to the drug's residual concentration is described by first-order kinetics. This strategy can be useful for providing quick initial release followed by a gradual fall in the setting of fast-dissolving buccal films.

The following is a representation of the drug release first-order kinetics equation:

$Ct=C0\ (1-e-kt)$ C_t = C_0 (1 - e^ {-kt}) $Ct=C0(1-e-kt)$

Or in logarithmic form:

$$\ln (C0-Ct) =-kt+\ln C0$$

Where:

- Ct = concentration at time
- C0 = initial concentration
- k = first-order rate constant
- t = time

This formula illustrates how the release diminishes with time and helps explain the relationship between the drug concentration and time.

B. Zero order

It explains a drug release mechanism in which the rate of release is fixed and unaffected by the drug's concentration. The following is an expression:

$$Ct=C0-kt$$

Where:

- Ct = concentration at time
- C0= initial concentration
- k = zero-order rate constant
- t= time

C. Higuchi model

This mathematical model is specifically utilized in the pharmaceutical sciences to explain how medications escape from a polymeric matrix. It was created by Torsten Higuchi in the early 1960s and is frequently used with films and tablets that are solid dosage forms.

The following formula represents a drug's release rate from a solid matrix:

Where Q is the dosage delivered, k is a system-dependent constant, and t is the duration of time.

$$Q=k\cdot t1/2$$

D. Korsemeyer-peppas model

A mathematical model that describes the drug release kinetics from polymeric materials, especially in formulations with controlled release. This model is especially helpful for comprehending the ways in which different elements influence the release mechanism.

The equation as:

$$M\infty Mt=k\cdot tn$$

Where:

- M∞ is the total quantity of drug in the system;
- T is the amount of drug released at time;
- K is a release constant; and
- N is the release exponent, which specifies the drug release mechanism.

RESULT AND DISSCUSSION

Preformulation studies

Table No. 5: Properties of sumatriptan succinate.

Test	Specification	Observation
Colour	White powder	White powder
Taste	Bitter	Bitter
Odour	Odourless	Odourless

Solubility

Table No. 6: Solubility of sumatriptan succinate.

Solvents	Inference
Water	Highly soluble
DMSO	Slightly soluble
Ethanol	Insoluble
Methanol	Sparingly soluble

Calibration curve of sumatriptan succinate

Table No. 7: Calibration of sumatriptan succinate.

Concentration(µg/ml)	Absorbance(nm)
0	0
2	0.150
4	0.286
6	0.413
8	0.548
10	0.698

The calibration curve of sumatriptan succinate was determined at 227nm by plotting on x-axis as concentration and y-axis as absorbance.

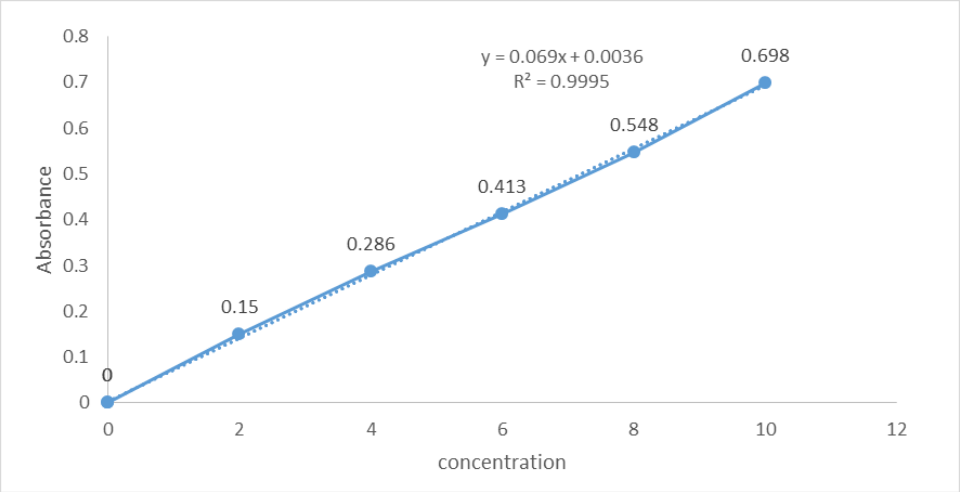

Figure No. 20: Calibration of sumatriptan succinate.

The absorbance values range from 0.150 at 2µg/ml to 0.698 at 10 µg/ml. The equation of the calibration line Y=0.068x+0.0043 with R^2 value of 0.9991 indicates a strong linear relationship between concentration (x) and absorbance (y).

FT-IR Analysis

FTIR is an essential technique for investigating drug-excipient interactions, providing insights that can help optimize formulation design and ensure drug efficacy and stability.IR spectra of samples were obtained by using FTIR-4600typeA spectrophotometer.

Sample 1: The FTIR spectrum of pure sumatriptan succinate exhibits absorption peaks at 3565.74 cm^{-1}, indicating N-H bond stretching associated with amines, at 1143.58 cm^{-1} corresponding to S=O stretching, and at 649.89 cm^{-1}, which is attributed to C-S stretching.

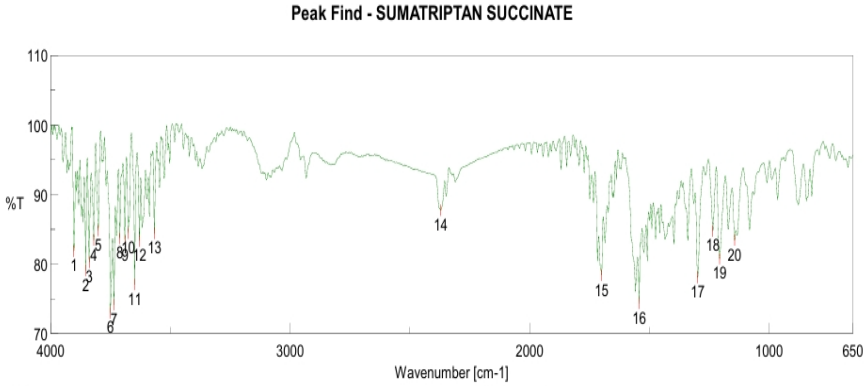

Figure No. 21: FTIR of sumatriptan succinate.

Sample 2: FTIR spectrum of HPMC E 15LV shows peak at 1080.91 cm^{-1} (C-O-H), 877.452 cm^{-1} (O-C), 1143.58 cm^{-1} (C-O,C-C), 1234.22 CM^{-1} (CH_2OH), 1339.32 cm^{-1} (C-O-H,CH_2), 3565.74 cm^{-1} (O-H).

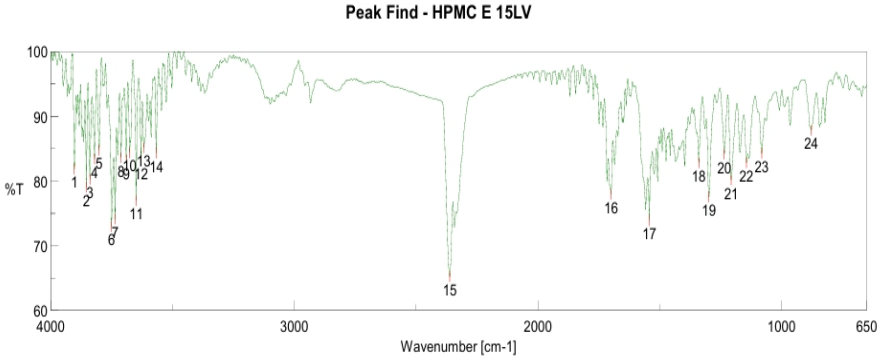

Figure No. 22: FTIR of HPMC E 15LV.

Sample 3: The FTIR spectrum of sodium carboxymethyl cellulose (CMC) shows distinct peaks at 1587.13 cm^{-1}, indicating C=O stretching in esters, at 1455.99 cm^{-1}, associated with the carboxylic acid (COOH) group, at 2669.96 cm^{-1} for C-H stretching, and at 3566.7 cm^{-1}, which corresponds to O-H stretching.

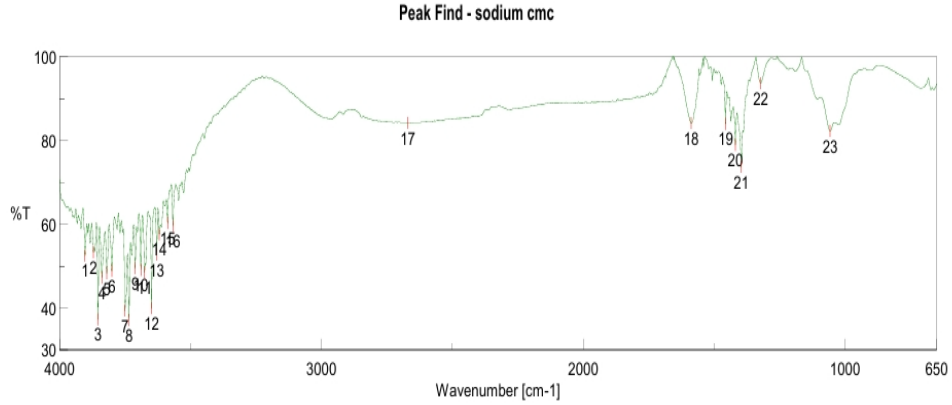

Figure No.23 FTIR of Sodium CMC.

Sample 4: The spectrum displays peaks at 1072.23 cm^{-1}, attributed to N-C stretching in amines, at 2920.66 cm^{-1}, corresponding to C-H stretching, and at 3445.21 cm^{-1}, indicative of O-H stretching.

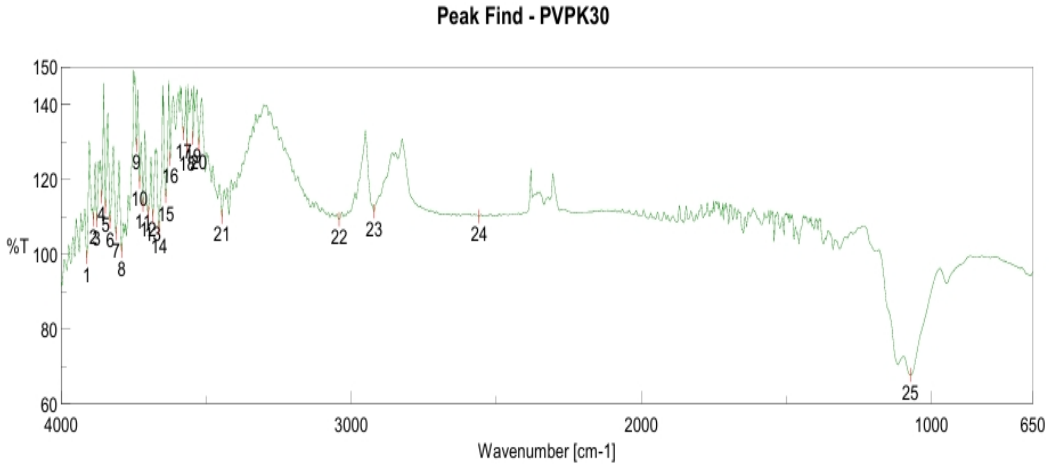

Figure No. 24: FTIR of PVP K 30.

Sample 5: The IR spectrum revealed notable peaks at 2920.66 cm^{-1}, corresponding to CH stretching in alkanes, at 1455.99 cm^{-1}, associated with CH bending, and at 3445.21 cm^{-1}, which is a characteristic peak indicative of hydroxyl (–OH) or amino (–NH) groups.

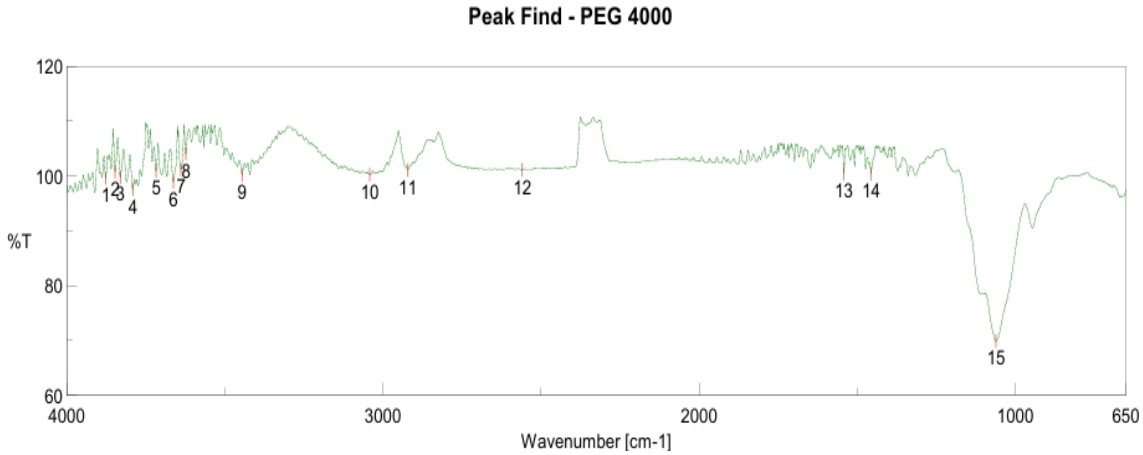

Figure No. 25: FTIR of PEG 4000.

Sample 6: This shows peak characteristic absorption bands of near 3000 cm^{-1} (C-H), 1700 cm^{-1} (C=O). The FTIR spectra of the drug and excipients exhibited no significant changes in peak positions, indicating that there are likely no strong interactions between the components. This suggests that the drug and excipients may remain chemically stable in the formulation. The absence of shifts or new peaks further implies that the functional groups of the drug are not significantly affected by the presence of the excipients, supporting the compatibility of the formulation components. Overall, the results indicate a lack of significant drug-excipient interactions that could impact the stability or efficacy of the final product.

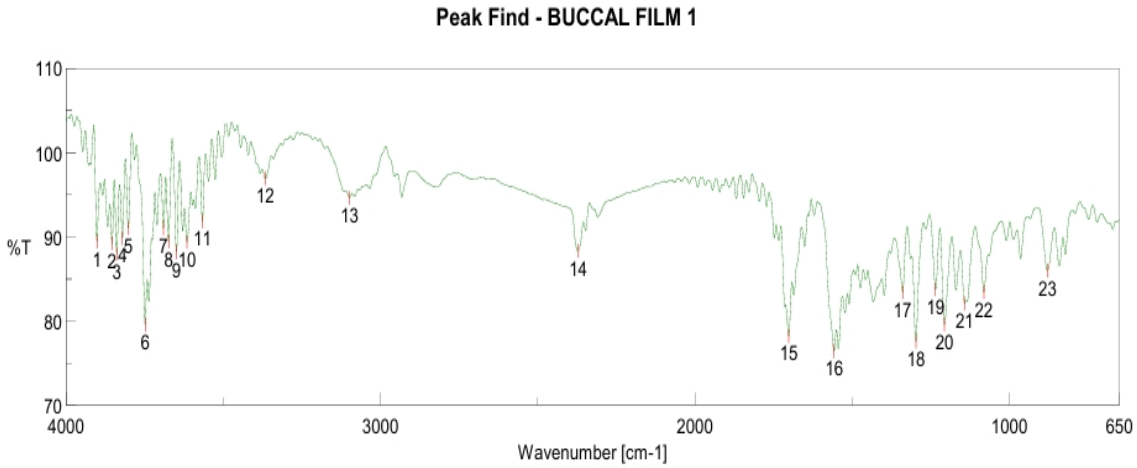

Figure No. 26: FTIR of buccal film.

Morphological characteristics

Table no. 8: Morphological characteristics of formulations.

Formulation code	Colour	Transparency	Homogeneity	Sense of touch
F1	No colour	Transparent	Homogenous	Smooth and dry
F2	No colour	Transparent	Homogenous	Smooth and dry
F3	No colour	Transparent	Homogenous	Smooth and dry
F4	No colour	Transparent	Homogenous	Smooth and dry
F5	No colour	Transparent	Homogenous	Smooth and dry
F6	No colour	Transparent	Homogenous	Smooth and dry
F7	No colour	Transparent	Homogenous	Smooth and dry
F8	No colour	Transparent	Homogenous	Smooth and dry
F9	No colour	Transparent	Homogenous	Smooth and dry
F10	No colour	Transparent	Homogenous	Smooth and dry
F11	No colour	Transparent	Homogenous	Smooth and dry
F12	No colour	Transparent	Homogenous	Smooth and dry

Table No.9 properties of formulations.

Formulation code	Weight variation	Thickness	Tensile strength
F1	0.0216±0.04	0.240±0.010	196.30±0.015
F2	0.0189±0.05	0.243±0.011	163.66±0.025
F3	0.0185±0.03	0.241±0.011	170.89±0.005
F4	0.0119±0.04	0.257±0.013	174.41±0.010
F5	0.0118±0.02	0.248±0.012	129.68±0.004
F6	0.0120±0.04	0.230±0.010	170.28±0.005
F7	0.0181±0.04	0.133±0.003	171.52±0.005
F8	0.0136±0.05	0.157±0.005	133.35±0.005
F9	0.0081±0.05	0.109±0.005	186.46±0.010
F10	0.0123±0.04	0.115±0.006	154.96±0.022
F11	0.0113±0.05	0.146±0.003	161.48±0.025
F12	0.012F9±0.05	0.246±0.011	132.71±0.005

Weight variation

The weight variation ranges from 0.0081 to 0.0216, with F1 having the highest weight variation and F9 the lowest. A lower weight variation generally indicates better uniformity in the formulation process, F9, F11, and F12.Higher variation in F1 and F2 may indicate slight inconsistencies in formulation.

Thickness

Thickness varies from 0.109mm to 0.257 mm, with F3 and F4 being the thickest and F9, F10 being thinnest. Thicker formulation like F3 and F4 might offer more structural integrity but could affect properties like flexibility, which may influence their performance in applications where folding endurance is important.

Tensile strength

The table shows data ranges from 129.68N/mm^2 to 196.30N/mm^2 .F4 stands out as having a relatively high tensile strength. Formulation F5,F12 and F8 have comparatively lower tensile strength ,which suggests these formulations are weaker in terms of mechanical resistance and might be more prone to breaking under stress.

Table No. 10 properties of formulations.

Formulation code	Folding endurance	%Moisture absorbance	%Moisture loss
F1	218±1.51	0.268±0.006	0.078±0.006
F2	195±1.30	0.233±0.004	0.059±0.001
F3	194±2.01	0.244±0.003	0.047±0.001
F4	200±1.32	0.221±0.004	0.041±0.001
F5	220±0.54	0.230±0.006	0.040±0.003
F6	218±0.52	0.249±0.004	0.061±0.005
F7	236±0.55	0.229±0.003	0.113±0.001
F8	238±1.35	0.225±0.005	0.130±0.006
F9	263±1.01	0.247±0.004	0.018±0.005
F10	248±0.89	0.232±0.002	0.144±0.004
F11	252±0.52	0.236±0.003	0.135±0.003
F12	240±0.81	0.224±0.006	0.137±0.006

Folding Endurance

A higher folding endurance value indicates better mechanical strength, which is essential for mataining the integrity of the buccal film during handling and application. F9 shows the highest folding endurance at 263 ± 1.01, indicating its superior mechanical properties. This suggests it may be more suitable for applications requiring durability. Generally, formulations F7, F8, F9, F10, and F11 have relatively high values, indicating that modifications made in these formulations may enhance mechanical properties.

% Moisture Absorbance

F1 has the highest moisture absorbance at 0.268 ± 0.006, suggesting it can retain more moisture, which could be beneficial for certain applications, such as in humid environments. The formulations F1, F6, and F9 demonstrate higher moisture absorbance, which may correlate with their material composition and structure.

% Moisture Loss

F9 also exhibits the lowest moisture loss at 0.018±0.005, which could be a concern for stability in applications where moisture control is critical. F5 and F4 show lower moisture loss, indicating better moisture retention properties, which could enhance the longevity of these formulations.

Surface pH test pH

Table No. 11 surface pH formulations.

Formulation code	pH
F1	6.93±0.015
F2	7.08±0.012
F3	6.90±0.008
F4	6.75±0.015
F5	7.02±0.022
F6	6.71±0.006
F7	6.73±0.015
F8	6.81±0.006
F9	6.86±0.008
F10	6.92±0.016
F11	6.95±0.015
F12	6.96±0.015

The pH values of the formulations (F1 to F12) provide insight into their chemical stability, compatibility with various applications, and potential effects on the performance of the materials. The pH of the formulations ranges from 6.71 (F6) to 7.08 (F2). All formulations fall within a slightly acidic to neutral range (approximately 6.71 to 7.08), which is generally favourable for many applications.F9 shows that the film remains stable and effective drug absorption through the buccal mucosa.

Content uniformity of drug

Table No. 12 content uniformity of drug for formulation.

Formulation code	Content uniformity
F1	85.63±0.016
F2	88.41±0.015
F3	89.14±0.014
F4	91.23±0.011
F5	72.57±0.011
F6	98.36±0.026
F7	96.63±0.011
F8	97.19±0.022
F9	98.86±0.022
F10	93.69±0.011
F11	94.53±0.026
F12	96.89±0.025

The content uniformity data for formulations F1 to F12 reflects the consistency of active ingredients or components within each formulation. This is crucial for ensuring efficacy, safety, and quality in product applications. The content uniformity percentages range from 85.63% (F1) to 98.46% (F9). F9 shows the highest content uniformity at 98.46 ± 0.022. This indicates excellent consistency in formulation, suggesting that it may provide more predictable performance.

Disintegration

Table No. 13: Disintegration time for buccal film.

Formulation code	Disintegration time
F1	6±2.00
F2	4±3.15
F3	3±2.50
F4	5±2.10
F5	6±3.05
F6	2±2.06
F7	3±2.20
F8	3±3.28
F9	2±2.08
F10	5±3.05
F11	4±2.14
F12	3±3.32

Disintegration times range from 2 minutes (F9) to 6 minutes (F5). Most formulations have disintegration times between 2 and 6 minutes, indicating relatively quick disintegration, which is generally desirable for optimal release of active ingredients. F9 shows the fastest disintegration time at 2 ± 2.08 minutes. This formulation may be ideal for applications where rapid release is critical. F5 has the longest disintegration time at 6 ± 3.05 minutes, which could delay the release of active ingredients and may be less desirable in contexts requiring prompt action.

Dissolution test

The dissolution test evaluates the release rate of the active pharmaceutical ingredient (API) from the buccal film, which is critical for ensuring proper absorption and therapeutic effectiveness. The provided data shows the release of active ingredients from formulations F1 to F12 at different time intervals (1 to 6 minutes). This type of data is essential for understanding the release kinetics of each formulation. F9 achieves the highest release at 98.76, indicating that this formulation may have superior release characteristics overall.

Table No.14 Dissolution test of all formulations.

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	44.6	17.8	10.3	13.32	13.85	17.7	19.9	10.6	34.74	29.22	34.1	42.08
2	46.4	26.4	27.0	22.0	21.4	35.8	24	13.6	58.9	41.56	36.4	49.26
3	47.5	39.4	35.7	36.0	32.00	49.4	26.4	22.4	74.32	43.9	59.6	59.11
4	59.2	41.8	42.0	45.0	44.6	69.6	30.9	45.0	85.2	46.4	64.2	64.1
5	71.9	66.6	44.2	53.2	55.4	79.8	64.4	53.2	93.2	77.46	80.04	65.4
6	74.6	85.2	76.3	80.4	67.8	96.2	90.4	80.0	98.76	81.4	81.0	95.04

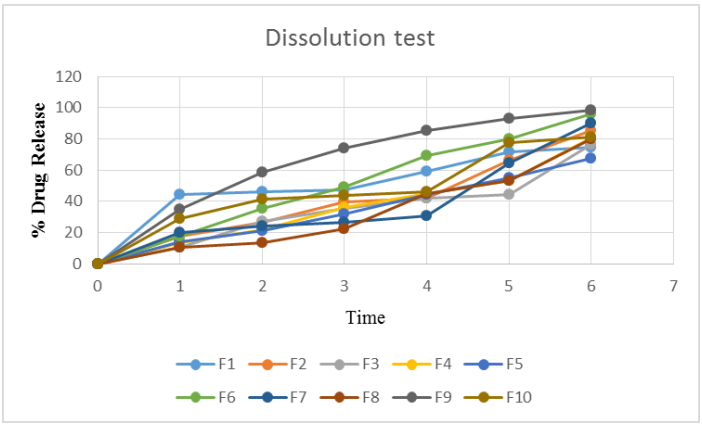

Figure No. 27: Comparative evaluation of % drug release.

Stability study of F9 formulation

The stability study of formulation F9 provides change over time. Here's a detailed analysis based on the data collected on the first day and after 90 days:

Table No.16 stability study of F9.

Temperature	Initial drug conc.	At1 month	At 2 month	At 3 month
5℃	98.86	98.86	98.82	98.82
30℃	98.86	98.86	98.84	98.82
45℃	98.86	98.85	98.83	98.83

The appearance remains unchanged, indicating that there are no visible signs of degradation or alteration in formulation integrity over the 3 months period. This is a positive indication of stability. There is a slight increase in disintegration time from 2 minutes to 6 minutes. This change, while minimal, suggests that the formulation may be experiencing slight alterations in its release properties. There is a notable decrease in drug content from 98.46% to 92.72%. This decline could indicate degradation or loss of active ingredients over the storage period. A slight decrease in folding endurance from 240 to 233 indicates that the mechanical properties of the formulation are relatively stable but may show minor wear over time. The slight change in weight uniformity is negligible, indicating consistent weight across the formulation over the 3 months.

Table No.14 Kinetics analysis of invitro release of formulation F9

Sl. No	Time (min)	Square root of time	Log time	Cumulative % Drug release	Log of cumulative % drug release	Cumulative % drug remain	Log of cumulative % drug remain
1	1	3.162	0	34.74	1.540	65.26	1.814
2	2	4.472	0.301	58.9	1.770	41.1	1.613
3	3	5.477	0.477	74.32	1.871	25.68	1.409
4	4	6.325	0.602	85.2	1.930	14.8	1.170
5	5	7.071	0.698	93.2	1.969	6.8	0.832
6	6	7.746	0.778	98.76	1.994	1.24	0.293

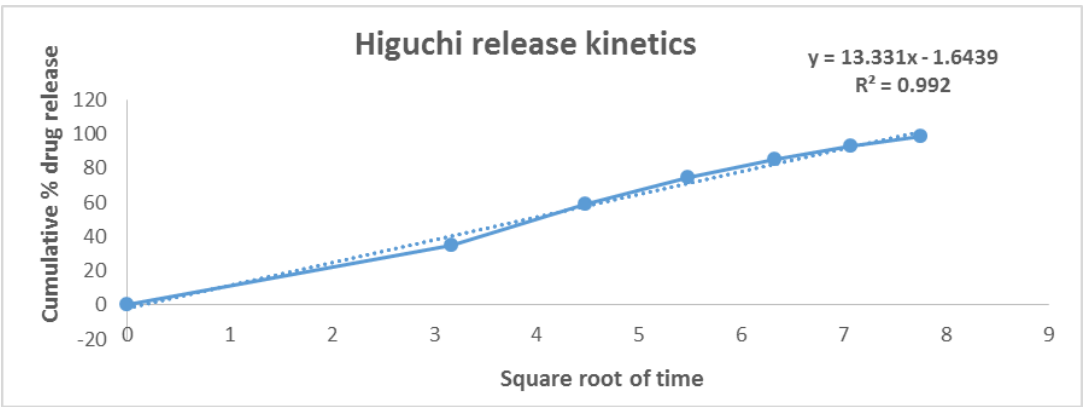

Figure No. 28: Higuchi release kinetics of formulation F9.

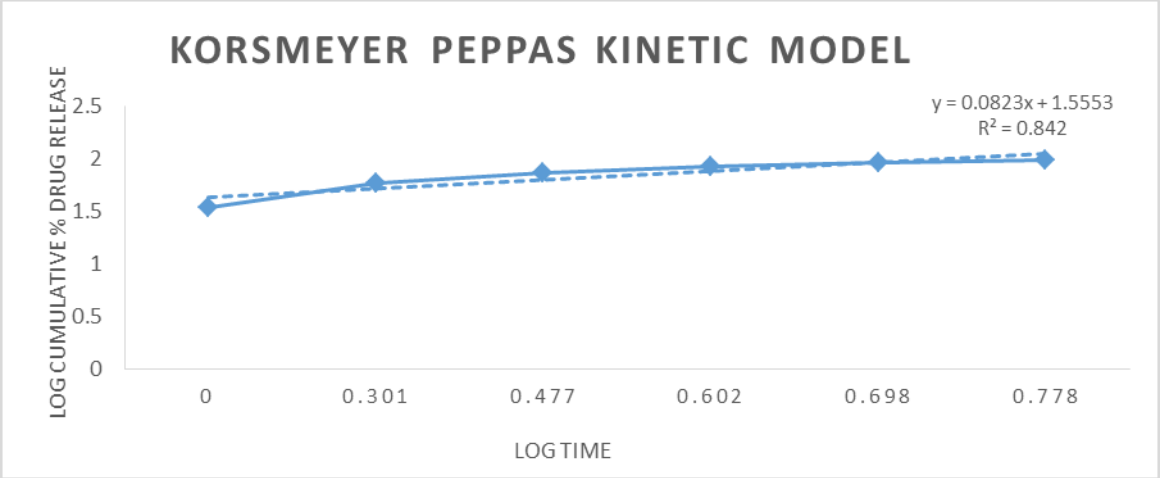

Figure No. 29: Korsmeyer peppas kinetic model of formulation of F9.

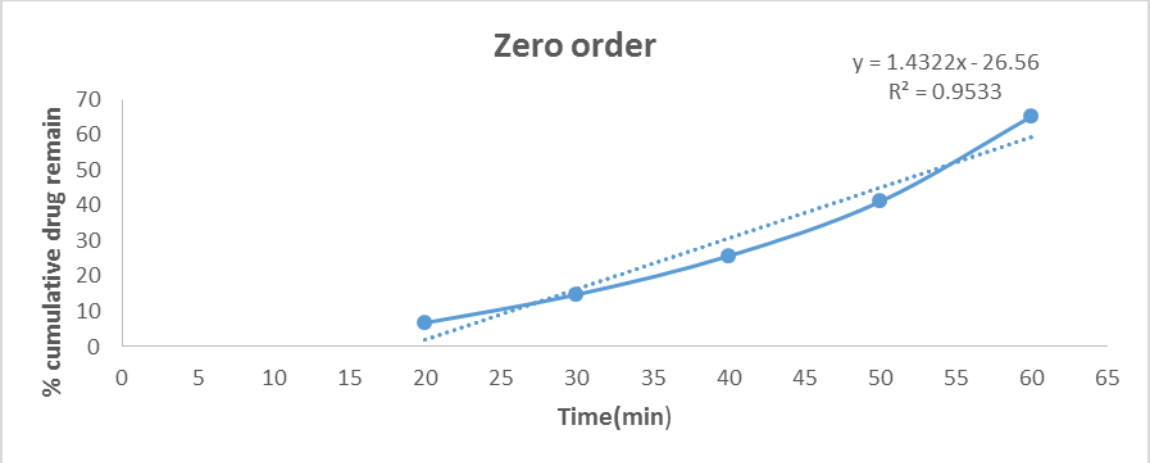

Figure No. 30: Zero order release kinetics of formulation F9.

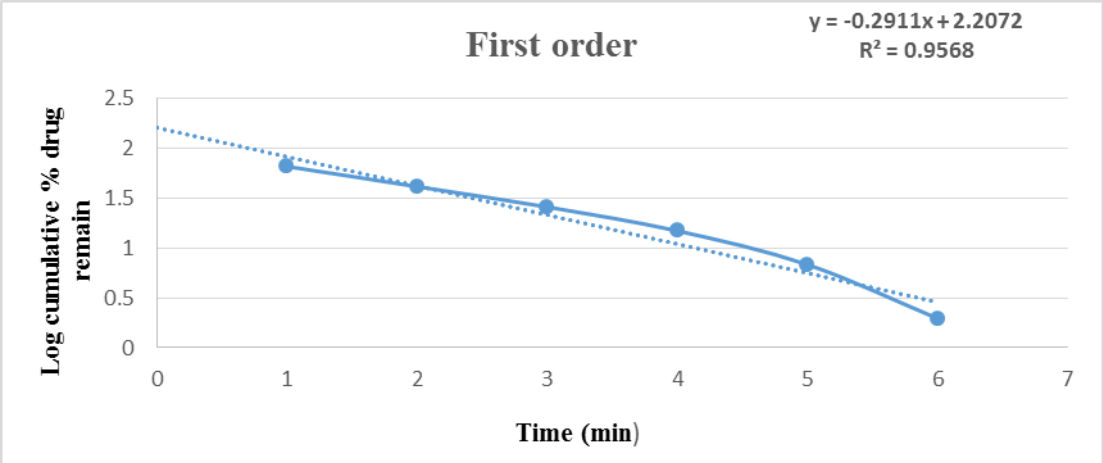

Figure No. 31: First order release kinetics of formulation F9.

Table no. 16: Kinetic data of optimized formulation F9.

FORMULATION CODE	REGRESSION COEFFICIENT	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS
F9	R^2	0.9533	0.9568	0.992	0.842

After undergoing the release model for optimized formulation the in vitro drug release of the optimized formulation F9 was best explained by first order, plots showed the highest linearity r^2 =0.9568,followed by zero order r^2=0.9533, Higuchi r^2 0.992 and korsmeyer- peppas r^2 0.842.

SUMMARY AND CONCLUSION

- Absorbance was measured at concentrations ranging from 0 to 10 µg/ml, showing a consistent increase in absorbance with higher concentrations. This demonstrates a linear relationship, confirming the assay's ability to accurately quantify sumatriptan succinate within this concentration range.
- FT-IR spectroscopy identified characteristic functional groups with no significant shifts, indicating compatibility between sumatriptan succinate and the chosen excipients, crucial for maintaining drug effectiveness and stability.
- Despite having the highest folding endurance, F9 also experienced considerable moisture loss, indicating a trade-off between mechanical strength and moisture retention.
- Content uniformity data revealed variability among the formulations, with F9, F8, and F7 demonstrating strong consistency and being promising options for applications requiring high reliability.
- Analysis of release profiles of F9 showed cumulative drug release versus the square root of time typically yields a straight line for Higuchi kinetics, were R^2 0.992, korsmeyer peppas kinetic drug release plot graph shows R^2 0.842.
- The disintegration time of Formulation F9 was the shortest at 2 minutes, and in kinetic release it achieved the highest cumulative drug release of 98.76% within 6 mins. These findings suggest that it is well-suited for rapid drug delivery, particularly beneficial for conditions requiring swift therapeutic action, such as migraine treatment.
- The stability study of Formulation F9 demonstrated acceptable stability over 3 months, with no changes in appearance. It is essential to continuously monitor these parameters, especially drug content, to ensure efficacy and safety.
- Additional stability studies over longer durations and under varying environmental conditions could provide more insights into the long-term stability of this formulation.
- With its impressive performance in drug release, achieving nearly complete release within 2 minutes, Formulation F9 appears to be a promising candidate for immediate-release formulations suitable for applications requiring a rapid onset of action.

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