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Formulation and evaluation of mouth dissolving sumatriptan buccinate films

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ABSTRACT

The aim of the study was to prepare the mouth dissolving films of sumatriptan succinate, which can useful in the acute attacks of migraine. The films were prepared by solvent casting technique. Mouth dissolving films were dissolved/disintegrated in the mouth with in a matter of few seconds without need of water. Various low viscous grades of hydroxy propyl methyl cellulose (HPMC) E15, E5, E6 and LVP K100 used as film forming polymers. Propylene glycol, sodium saccharine and sorbitol are used as plasticizer and sweetening agents respectively. The prepared films were evaluated for thickness, content uniformity, folding endurance, *invitro*, *in vivo* disintegration time and *in vitro* release studies. *In vitro* and *in vivo* disintegrated studies of all films revealed that disintegrates with in 35-90 seconds. *In vitro* release studies showed 90% of drug release from all formulations within 15 minutes. The films were flexible at 20% of plasticizer concentration. Drug was uniformly distributed throughout the film and adequate thickness for handling. The formulation containing HPMC E5 (2.5%) showed better performance in terms of disintegration time and percent drug release profile. This finding suggests that the mouth dissolving films were likely to become one of the choices of sumatriptan succinate preparations for migraine therapy.

INTRODUCTION

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity [1].

Developing formulations for children has been a challenging task. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens (Crama et al.,2009; Florence et al., 2008). Although solid dosage forms are widely accepted by elders and adolescents, younger children tend to prefer liquid formulations that are easier to swallow. Keeping the ease of administration and swallowing in mind, pharmaceutical research has led to the development of Oral Disintegrating Tablets (ODTs). ODTs have been defined as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". United States Food and Drug Administration further defines ODTs as solid oral

preparations that disintegrate rapidly in the oral cavity, with an in- vitro disintegration time of approximately 30s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.

Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral strip (OS). Basically the OS can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other excipients. The advantages of convenience of dosing and portability of OS have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally. The introduction of ODT in market was accompanied by educating the mass about the proper way to administer the product like giving instructions "do not swallow" or "do not chew".

ANATOMIC AND PHYSIOLOGIC FEATURES OF THE ORAL CAVITY

The surface area of the oral mucosa is about 100 cm^2. Three different types of oral mucosa are recognized: the mucosa, the lining mucosa, and the specialized mucosa. The masticatory mucosa, representing 25% of the total oral mucosa, is100–200µm thick and covers the gingiva and the hard palate. It is tightly attached to underlying structures and subjected to abrasion and shear stress during mastication. The lining mucosa (60% of the total oral mucosa) is 500–800µm thick and covers the lips, cheeks, soft palate, and lower surface of the tongue and the floor of the oral cavity. The specialized mucosa (15% of the total oral mucosa) is present on the dorsum of the tongue and is involved in taste [2-5].

Buccal Epithelium

The buccal epithelium is a non-keratinized stratified squamous epithelium, composed of multiple layers of cells that show different patterns of maturation between the deepest cells and the surface. The basal cells of the buccal epithelium are capable of division and maintain a constant epithelial population as cells move toward the surface. Tissue homeostasis requires differentiation followed by migration and desquamation of the superficial cells. The prickle cells (intermediate layer) accumulate lipids and cytokeratins of low molecular weight that do not aggregate to form filaments. An intracellular lipid portion is packaged in small organelles called membrane coating granules or lamellar granules. 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 space. The buccal epithelium lacks tight junctions, which are common to intestinal and nasal mucosa, but is endowed with gap junctions, glydesmosomes and hemidesmosomes, which are loose intercellular links. The epithelium rests on the basal membrane, 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 occur when the drug is released in the oral cavity in contact with buccal mucosa. The drug transport mechanism through the buccal mucosa involves two major routes

- Transcellular (intracellular)
- Paracellular (intercellular)

The transcellular route involves passage through the cellular membranes with a polar and a lipid domain,while the paracellular route essentially consists of passive diffusion through the extracellular lipid domain. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway, especially with compounds that are hydrophilic and have a high molecular weight, such as peptides.

Visualization of the Oral Mucosa

Arterial, venous and lymphatic capillaries penetrate the multi- layered epithelium, infiltrating the connective tissue. The oral mucosa is primarily supplied by the external carotid artery, which serves the large buccal blood vessels. The floor of the mouth, the root of the tongue and the cheek mucosa are the most highly vascularized areas. Vascular drainage from the oral mucosa is primarily via the lingual, facial and retromandibular veins, which flow together into the internal jugular

vein. This is the mechanism responsible for by passing first-pass hepatic metabolism [6].

Salivary Flow

Saliva is the medium for disintegration or dissolution for drug formulations designed to disintegrate/dissolve in the oral cavity; for this reason, the properties of saliva are crucial to oral fast-dissolving tablets. The saliva is primarily secreted in the oral cavity by parotid, submandibular and sublingual glands, and also by numerous minor glands. The main constituent of saliva is water (99.5% w/v). The remaining 0.5% w/v consists of dissolved compounds; in fact, saliva is a hypotonic solution (150–200 mOsm) compared with extracellular fluids (300 mOsm). The principal components of saliva are: inorganic electrolytes (0.2% w/v), including sodium, potassium, calcium, magnesium, bicarbonate and phosphates; gases (carbon dioxide, nitrogen, oxygen); nitrogen products such as urea and ammonia; ascorbic acid (vitamin C); creatinine; and mucins (high-molecular-weight glydesmosomes co proteins, which render the saliva viscous and adhesive). Saliva also contains amino acids and proteins, digestive enzymes(salivary α-amylase[ptyalin],lipase,maltase,and lysozyme with antibacterial activity), proteolytic enzymes (moderate levels of esterase, carbohydrates and phosphates), serum albumin and immunoglobulin. Saliva has a weak buffering capacity and its normal pH value is slightly acid (pH 6–7); however, salivary flow pH can range from 5.3 (low flow) to 7.8 (peak flow). The accepted range of normal salivary flow is approximately 0.1–0.2 mL/min, increasing to 7 ml/min upon stimulation. Saliva wets the entire oral cavity and the resulting mucus layer ranges from 1 to 400µm in thickness, forming a physical barrier to drug permeation and a useful substrate for mucoadhesive drug delivery systems.

FORMULATION CONSIDERATIONS

Formulation of Oral Strips involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc [7].

Strip forming polymers

A variety of polymers are available for preparation of OS. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation (Corniello et al., 2006). As the strip forming polymer (which forms the platform for the OS) is the most essential and major component of the OS, at least 45%w/w of polymer should generally be present based on the total weight of dry OS (Frankhauser et al., 2007). Of the various polymers available, pullulan, gelatin and hypromellose are most commonly used for preparation of OS. Typically 60 to 65%w/w of water soluble polymer is preferred for preparation of OS with desired properties (Lydzinski, et al., 2003; Kulkarni et al., 2003). Many times, mixtures of polymers are used to improve hydrophilic, flexibility, mouth-feel and solubility characteristics of OS. Polyvinyl pyrrolidone films are brittle in nature and therefore copovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating strips (Ali et al., 2007). The polymer employed should be non- toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive.

Plasticizers

Plasticizer is a vital ingredient of the OS formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer (Sakellariou et al., 1995; Banker et al., 1966).Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as

tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20%w/w of dry polymer weight (Indoe et al., 2006; Kennedy et al., 2006).However inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip (Rowe et al., 1980, 1966). It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug (Sing et al., 1966) [8, 9].

Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. The classical source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and maltose. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are also less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients (Mennella et al., 2008; Hutteau et al., 1998).

Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200–300 time sweetness (Prakash et al., 2008 ; Sharma et al., 2007).Generally sweeteners are used in the concentration of 3 to 6%w/w either alone or in combination (Sau et al., 2003).

Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.

Flavoring agents

It was observed that age plays a significant role in the taste fondness.Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple is few examples of fruit essence type.The amount of flavor needed to mask the taste depends on the flavor type and its strength.

Preferably up to 10%w/w flavors are added in the OS formulations.

Coloring agents

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in OS when some of the formulation ingredients or drugs are present in insoluble or suspension form (Obermeir et al., 2008).

TECHNOLOGIES USED IN THE MANUFACTURE OF MOUTH DISSOLVING FILMS

One or combination of the following process can be used to manufacture the mouth dissolving films (Mishra et al.,).

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

Films can be prepared either by hot melt extrusion method or solvent casting technique. In the extrusion process the API and other ingredients are mixed in dry state, subjected to heating process and then extruded out in molten state. In this process, solvents are completely eliminated. The strips are further cooled and cut to the desired size. The high temperature used in this process may degrade thermolabile APIs. Hence, generally the solvent cast method is employed for manufacture of strips (Figure 1).

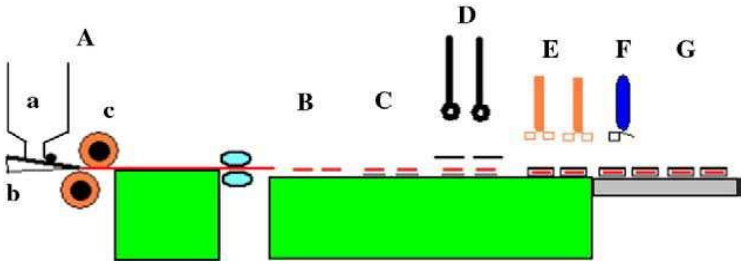


Figure 1. Schematic representation of a typical OST manufacturing unit.

A – Formation of medicated film takes place. The rollers can be adjusted to get the desired film thickness. After formation of film, it is dried. a – Reservoir for the filmformingmaterials, b – deaerator and film applicator, c – rollers. B – The driedmedicated film is slit and cut into little strips of desiredsize. C – Strips are placedinto lower packagingweb.D– Laser printer prints on upper packagingweb. E – Sealing head seals the strips into single dose sachets. F – Introduction of tear-notch/slit/cut off to sachet. G – Quality control conveyer to final packaging.

Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both.

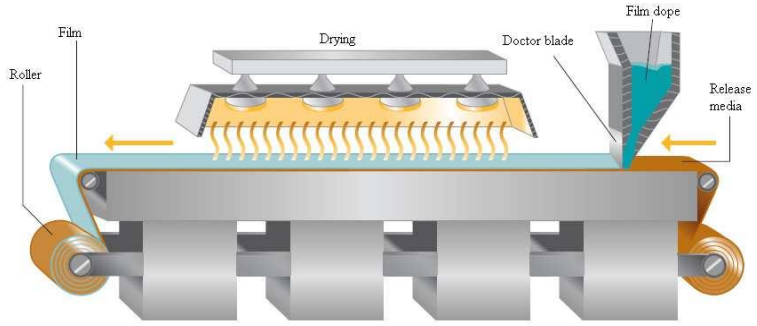
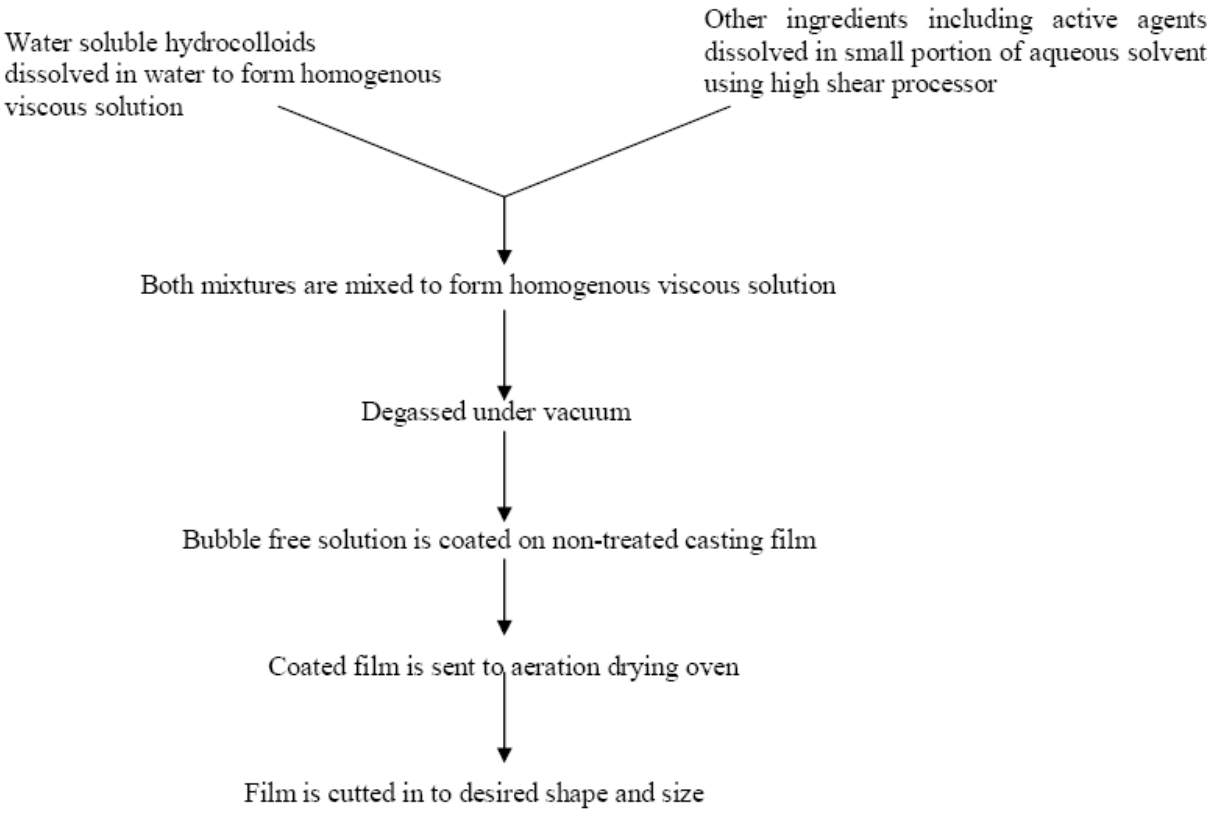


Figure 2. Solvent casting film system



Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion (Coppens et al., 2005).

- Fewer operation units
- Better content uniformity
- An anhydrous process the solutions are mixed and stirred and finally casted in to the

Petri plate and dried.

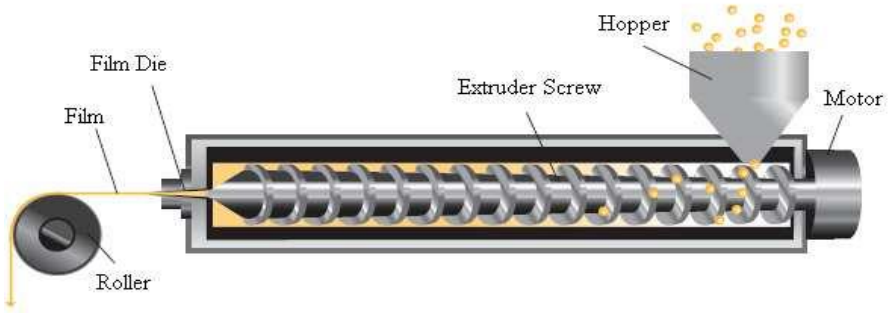


Figure 3 Film Extrusion systems

Semisolid casting

In semisolid casting method firstly a solution of watersoluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The

ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared.Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes (Frey et al., 2006).

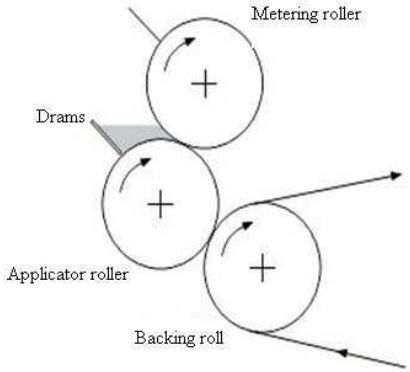


Figure 4. Three roll coating unit

PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING FILMS

Soluleaves™

SOLULEAVES™ technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

Wafertab™

WAFERTAB™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The WAFERTAB™ filmstrip can be flavoured for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre- manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty swallowing.

Foamburst™

FOAMBURST™ is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.

Xgel™

XGEL™ film is at the heart of Meldex International's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is nonanimal derived, approved on religious grounds and is suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing platform. XGEL™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use. All of the XGEL ingredients are well known and generally regarded as safe (GRAS).

DRUG PROFILE SUMATRIPTAN SUCCINATE

Description

A serotonin agonist that acts selectively at 5HT1 receptors. It is used in the treatment of migraine disorders.

Chemical IUPAC Name: 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1)

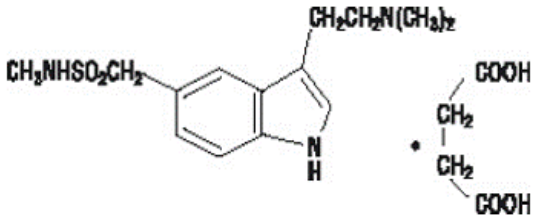
Empirical Formul : $C_{14}H_{21}N_3O_2S•C_4H_6O_4$

Molecular weight : 413.5

Physical state : A white to off-white powder

Solubility soluble in water and in saline Melting point: 169-171°C

Structure



Indications

Indicated for the acute treatment of migraine attacks with or without aura in adults. This is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine.

Mechanism of Action

Sumatriptan Succinate stimulates 5-HT receptors of the 1D subtype, most likely presynaptic receptors, resulting in selective vasoconstriction of inflamed and dilated cranial blood vessels in the carotid circulation. Sumatriptan also blocks the release of vasoactive neuropeptides from perivascular trigeminal axons in the dura mater during migraine and may inhibit the release of inflammatory mediators from the trigeminal nerve.

Toxicity

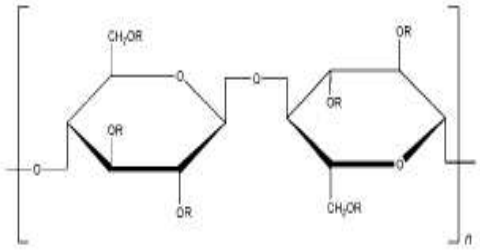
Symptoms of overdose include convulsions, tremor, paralysis, inactivity, and ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly Omethylated and O-(2- hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3).

The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000.

Structural Formula



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder (Chowhan et al., 1980), in film-coating (Rowe et al., 1977; Banker et al., 1981; Okhamafe et al., 1982; Alderman et al., 1989; Patell et al., 1990) and as a matrix for use in extended-release tablet formulations.(Hardy et al., 1982; Hogan et al., 1989; Shah et al., 1989; Wilson et al., 1989; Dahl et al., 1990) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher- viscosity grades are used with organic solvents. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

Nonproprietary Names

BP: Propylene glycol JP: Propylene glycol PhEur: Propylenglycolum USP: Propylene glycol

Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics. As an

antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations. Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor.

Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving. Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

METHODOLOGY

Construction of Standard Graph in 6.8 pH Phosphate Buffer Solution

Accurately weighed amount (100mg) of the drug was dissolved in 20ml of phosphate buffer solution in 100ml volumetric flask and the volume made up to 100ml.From the stock solution (1mg/ml) 10 ml of solution was withdrawn and poured in to 100ml of volumetric flask and the volume was made with phosphate buffer. From this second stock solution (100µg/ml) corresponding dilutions were made to get concentration of 2, 4, 6, 8, 10 µg/ml and their absorbance was analyzed at 228 nm using UV/Visible spectrophotometer.

Preparation of Mouth Dissolving Films

The films were prepared by solvent casting method. Briefly, HPMC was dispersed in water and then soaked for 4 hours. The propylene glycol, sodium saccharine and Sorbitol are dissolved in 5ml of 50% v/v ethanol. Alcoholic and polymer dispersion were mixed together to obtain a homogeneous dispersion, this was poured on to a Petri plate and dried for 60°C. The films were carefully removed from Petri plate and cut into strips of 2X2 cm^2 dimensions. Stored in glass bottle.

Physicochemical Characterization

Fourier Transform Infrared Spectroscopy (FTIR)

Samples were prepared in KBR disks and the infrared spectra of Sumatriptan succinate, HPMC E5, Physical Mixture of Sumatriptan Succinate and HPMC E5 were recorded at a scanning range of 400 to 4000 cm^{-1}

Differential Scanning Calorimeter (DSC)

Samples were heated in an open aluminum pan in ranges of 30-300°C and characteristic thermo grams were recorded for Sumatriptan Succinate, HPMC E5, and Optimized Formula.

Morphological Studies

Scanning Electron Microscopy

The surface morphology of blank strips and strips containing sumatriptan succinate was observed under scanning electron microscopy (Mashru et al., 2005).

QUANTITATIVE COMPOSITION OF MOUTH DISSOLVING FILMS

Table 1. Composition of Sumatriptan Succinate containing Mouth dissolving films.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Sumatriptan succinate	397.75	397.75	397.75	397.75	397.75	397.75
HPMC E15	500	700	900	-	-	-
HPMC E5	-	-	-	500	700	900

HPMC LVPK1OO	-	-	-	-	-	-
HPMC E6	-	-	-	-	-	-
Propylene glycol	0.096	0.135	0.175	0.096	0.135	0.175
Ethanol	5ml	5ml	5ml	5ml	5ml	5ml
Sodium saccharine	300	300	300	300	300	300
Sorbitol	100	100	100	100	100	100
Water	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml

Ingredients (mg)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Sumatriptan succinate	397.75	397.75	397.75	397.75	397.75	397.75
HPMC E15	-	-	-	-	-	-
HPMC E5	-	-	-	-	-	-
HPMC LVPK1OO	500	700	900	-	-	-
HPMC E6	-	-	-	500	700	900
Propylene glycol	0.096	0.135	0.175	0.096	0.135	0.175
Ethanol	5ml	5ml	5ml	5ml	5ml	5ml
Sodium saccharine	300	300	300	300	300	300
Sorbitol	100	100	100	100	100	100
Water	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml	Upto 20ml

Evaluation of Prepared films

Thickness

The six strips from the film was randomly taken, thickness of strip can be measured by using digital verneir calipers at different strategic locations. Average thickness and standard deviation values were calculated.

Weight Variation

To study the weight variation, individual weights (W_I) of strips from each formulation were noted by using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as fallows

Percent weight variation = $\frac{(W_A - W_I) \times 100}{}$

In- Vitro drug release studies

The in vitro release studies can be performed according to USP XVIII apparatus II, paddle method utilizing dissolution system (electro lab, India). Paddle speed was maintained at 50 rpm and 900mL of 6.8 pH phosphate buffer as the dissolution medium at a temperature 37±0.5°C. Samples were collected at pre determined time intervals of 5, 10, 15, 30, 45, 60, 90 minutes and replaced with equal volume of fresh medium. The solution was filtered and analyzed with UV/Visible spectrophotometer at 228nm (Mashru et al., 2005). Concentration of drug calculated from standard calibration curve from that percent drug release was noted.

Disintegration time

The disintegration time was determined by the following procedure, 10ml of water was poured in 6cm Petri plate, the strip was placed in the centre of the Petri plate. The time required for the strip to disintegrate completely was noted. Measurements were carried out in replicates (n=6) and mean ± S.D values were recorded.

Content uniformity

To determine content uniformity, four strips at different locations were taken from the film and these strips were dissolved in 100ml of 6.8 phosphate buffer solution. The solution was centrifuged at 3000rpm for 15min then the supernatant was taken and absorbance was noted spectrophotometrically at 228nm.The drug content was calculated by using the standard calibration curve.

Folding endurance

To the prepared films, the folding endurance was measured manually. Six strips of dimensions (2X2) cm2 were cut from the film. Strips from the film was randomly taken and repeatedly folded at the same place till it breaks. The number of times the strip could be folded gives the value of folding endurance (Devi et al., 2003).

In vivo disintegration time

In vivo disintegration time was performed in six healthy volunteers for the optimized formulations. All volunteers were asked to rinse their mouth before commencement of the study, each volunteer was given the formulation and allowed to place the strip on tongue and asked to gently press the strip to upper palate of mouth with tongue. The time taken for the strip to disintegrate was noted.

RESULTS AND DISCUSSION

HPMC is a film former, having excellent film forming ability (Peh et al., 1999). Initial studies indicated that the film gave desired properties at a concentration of 2.5% w/v. To improve the palatability of the mouth dissolving films the natural sweeteners, artificial sweeteners are used in combination. Mannitol and Sorbitol was used as natural sweeteners. These agents were expected to give more cooling sensation in the mouth (Mennella et al., 2008). Incorporation of mannitol resulted in white patches where as the Sorbitol containing films showed good film characteristics. So, Sorbitol was selected as natural sweetener in this formulation (Prakash et al., 2008). However one more advantage with Sorbitol is its high negative heat of solution. The artificial sweetener used in the preparation was Sodium saccharine but its disadvantage was after the taste effect. This can be reduced by mixing with the natural sweeteners. Plasticizers were used to maintain the flexibility of the films. Among the various plasticizers the propylene glycol was found to be better when compared to glycerol. The glycerol used formulations resulted in sticky films.

Standard graph

Standard graph of Sumatriptan succinate in 6.8 pH phosphate buffer at λ_{max} 228 nm was plotted and good correlation was obtained with R^2 value of 0.999

Table 2. Standard graph of sumatriptan succinate in pH 6.8 Phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.234
4	0.440
6	0.656
8	0.867

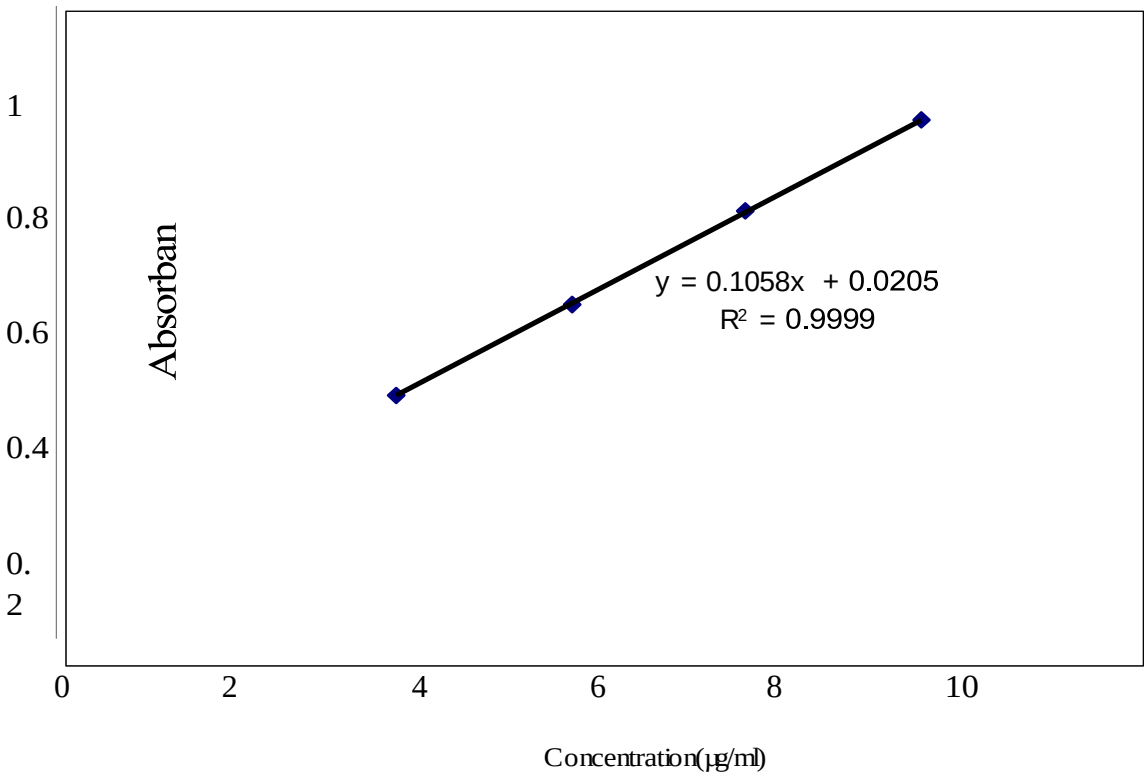


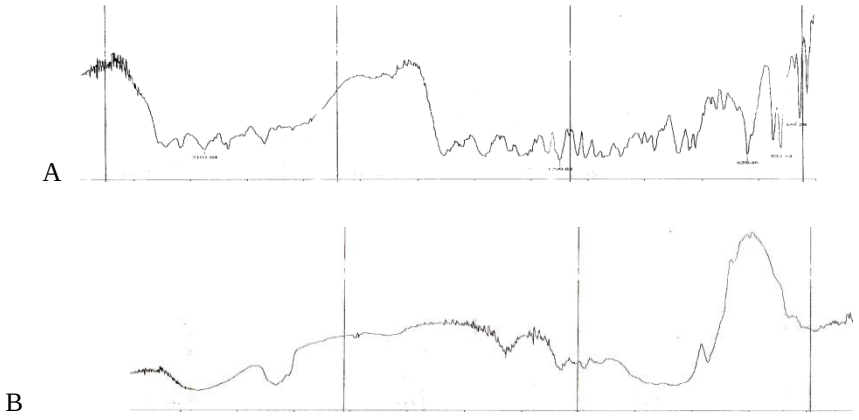
Figure 5. Plot of Standard graph of sumatriptan succinate in pH 6.8 Phosphate buffer.

Physico chemical Characterization

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed to detect the possible molecular interaction between Sumatriptan Succinate and HPMC E5 in the drug polymer complex. FTIR spectra of Sumatriptan Succinate, HPMC E5, and its physical mixture were presented in Figure

The Characteristic peaks of Sumatriptan Succinate appear in the spectra of physical mixture at a same wave number as that of drug indicating no interactions between drug and carrier.



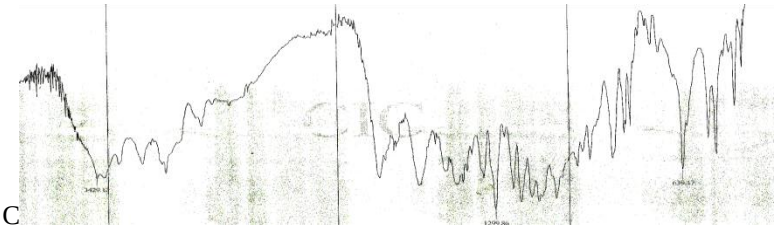
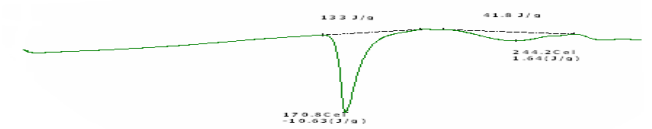
C 

Figure 6. FTIR spectra of (a) Sumatriptan succinate, (b) HPMC E5, (C) Physical mixture.

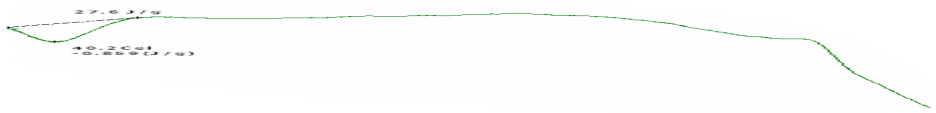
Differential Scanning Calorimeter (DSC)

DSC curves of pure drug, polymer and film containing sumatriptan succinate was shown in figure 7. Sumatriptan succinate showed endothermic peak at 170.8°C. Corresponding to its melting point and the polymer showed peak at 40.8°C. The film containing Sumatriptan succinate showed two peaks, one at 72.6°C corresponding to polymer, and another at 157.8°C. DSC peaks of film indicate that, drug did not interact with polymer.

A)



B)



C)

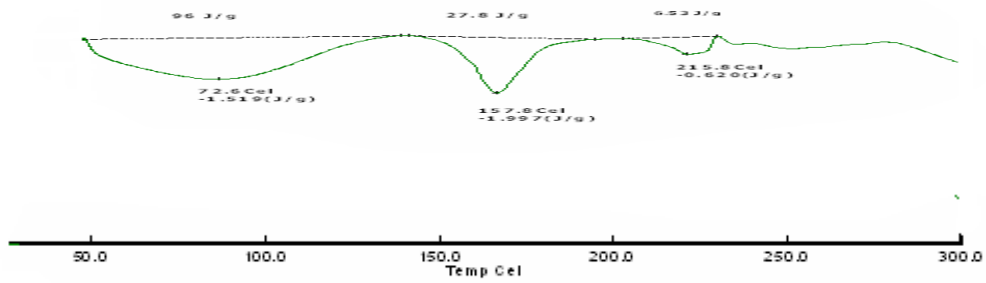
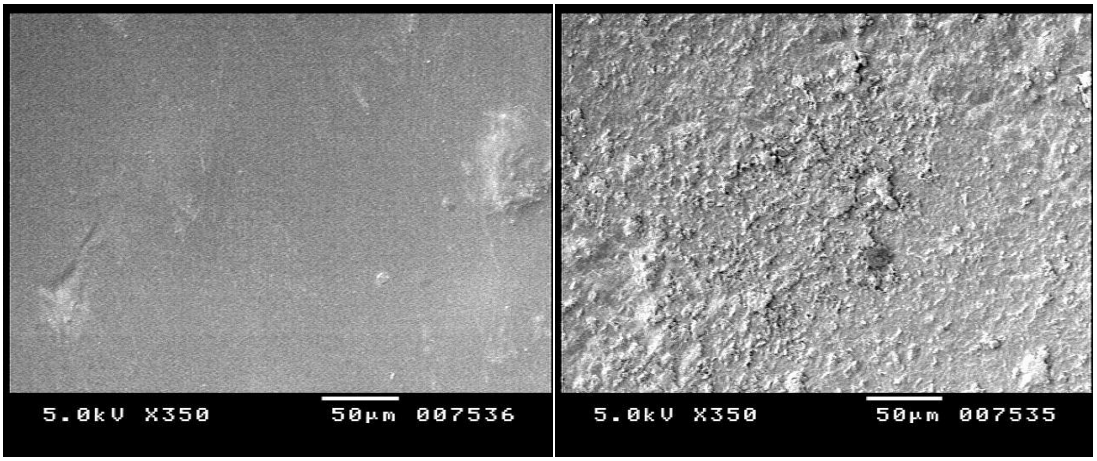


Figure7.DSCthermogramsofA)Puredrug,B)Polymer,C)Optimized formula of drug polymer complex.

Scanning Electron Microscopy

The surface morphology of blank strips and strips containing sumatriptan succinate was observed at 350 X magnification showed that, the drug was uniformly distributed.

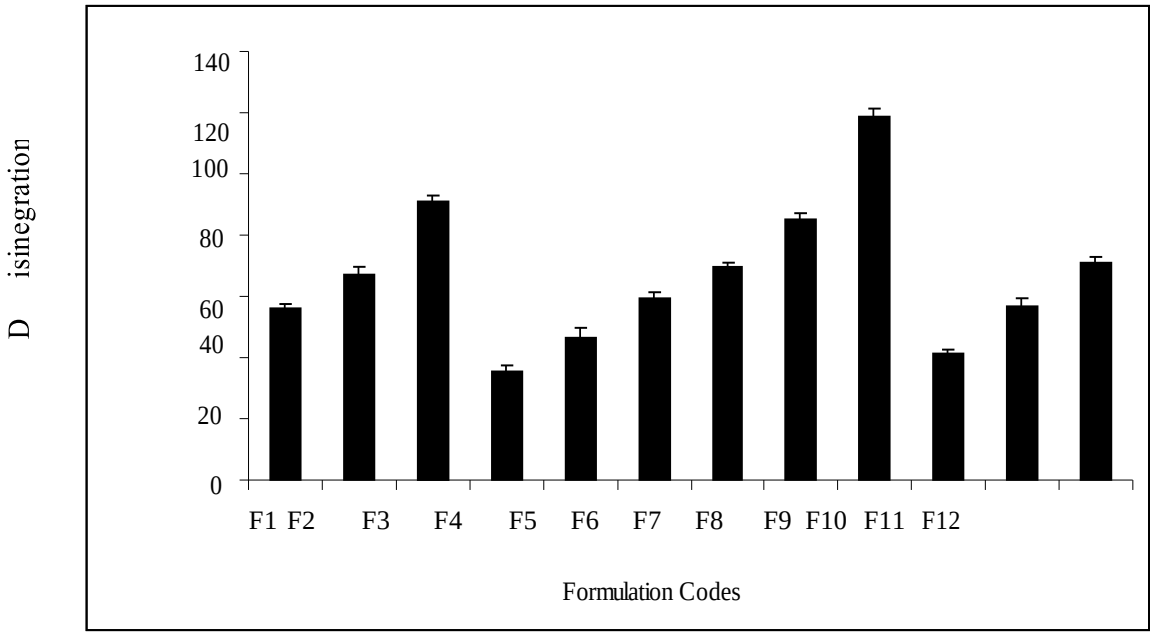


A **B**

Figure 8. SEM Photographs of A) HPMC E5 strip, B) Sumatriptan Succinate containing strip.

Disintegration time

One of the most important characteristics of the mouth dissolving films was its disintegration time (Narazaki et al., 2004). The disintegration test was performed for all the formulations. Formulations with the higher amount of polymer (3.5%) had high disintegration time as per the (table 3). Almost all formulations were disintegrated in less than 2min. The F4 Formulation disintegrated rapidly within 36s. *In vivo* disintegration time was performed in human volunteers (n=6) and the disintegration time (achieved at 48.07, 49.37, 51.08, 46.55, 52.56, 50.5 sec) respectively and mean was 50sec.



Content Uniformity

Uniformity of drug content was estimated for all the formulations. Formulations were found satisfactory in uniformity of drug.This indicates the drug was uniformly distributed and results were given in the table.

Table 3. Evaluation Parameters of Sumatriptan Succinate Films.

Formulations	Weight(mg)	Thickness (mm)	Folding Endurance	Content uniformity	Disintegration Time
F1	70.35±2.78	0.28±0.02	143.00±7.00	99.43±0.55	56.19±0.98
F2	90.12±0.75	0.35±0.06	192.00±7.21	98.60±2.52	66.86±2.55
F3	110.4±2.74	0.41±0.01	201.33±3.21	99.43±0.83	91.13±1.65
F4	60.72±1.21	0.17±0.03	95.00±5.57	100.63±0.02	35.49±1.89
F5	75.53±1.88	0.23±0.02	184.33±5.03	99.8±1.63	46.68±3.15
F6	95.65±1.84	0.31±0.02	200.67±4.51	98.33±2.99	59.33±2.09
F7	80.63±2.36	0.25±0.01	181.33±6.11	99.46±1.56	69.52±1.42
F8	99.56±3.03	0.36±0.01	99.00±13.53	100.1±0.23	85.04±2.30
F9	118.8±2.56	0.44±0.03	235.33±5.03	99.06±2.56	118.39±2.91
F10	62.32±1.56	0.17±0.01	98.00±3.00	98.35±1.55	41.38±1.18
F11	78.20±2.30	0.26±0.02	176.00±6.08	99.68±2.30	56.80±2.64
F12	98.65±0.80	0.34±0.02	211.67±10.41	98.36±1.50	70.87±2.21

In - vitro Drug Release Profile

In vitro drug release profile of mouth dissolving strips at different concentration of HPMC E15

An Increase in concentration of polymer resulted in decreased cumulative percent drug release of three formulations. F1 released 100.62% of the drug within 15 min, F1, F2, F3 released 77.42±2.54, 52.30±2.65, 58.96±0.35 of drug at 5min respectively.

Table 4. *In- vitro* drug release profiles of F1, F2, and F3 formulations

Time (min)	F1	F2	F3
0	0	0	0
5	77.42±2.54	58.96±0.35	52.30±2.65
10	87.70±2.65	81.86±1.93	73.10±1.46
15	99.74±0.88	86.89±2.46	83.15±2.30
30	97.29±1.58	97.40±2.11	89.81±2.63
45	90.63±2.14	87.70±4.82	99.51±1.66
60	84.55±2.78	84.20±2.65	95.18±3.86
90	82.10±2.13	83.85±3.71	89.34±3.51

SUMMARY

- Mouth dissolving sumatriptan succinate films were success fully prepared by using solvent casting method.
- FTIR reports showed no interaction between drug and polymer as characteristic peaks of drug remained same in the spectrum of physical mixture of drug and polymer.
- DSC studies conformed that, the intensity of both endothermic and exothermic peaks of drug were less in drug polymer complex compared to pure drug indicated the amorphorization of drug crystallinity.
- SEM results proved that the film containing sumatriptan succinate was uniformly distributed.
- All the strips were evaluated for different parameters like, thickness, weight variation, in- vitro drug release profile, *in vitro* and *in vivo* disintegration time and content uniformity.

CONCLUSION

Mouth dissolving films are interesting novel dosage forms and their use will definitely expand in the future. The films could be formulated with easily available components such as HPMC and propylene glycol by solvent casting method. The preparations revealed excellent uniformity, thickness, dissolution profile and disintegration. Formulation F4 considered as optimum due to its low in-vitro and in-vivo disintegration and maximum drug release compare to other formulations. So these studies showed that mouth dissolving films are innovative dosage forms to improve the delivery of sumatriptan succinate for migraine treatment.

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