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Review Article

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Formulation and Evaluation of Fast Dissolving Sublingual Films

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ABSTRACT

The fast dissolving sublingual films were obtained by the solvent casting method. It showed acceptable mechanical properties and satisfactory drug release. The prepared film was transparent with smooth surface without any drug excipients interaction. The multiple regression analysis of the results led to such equations that describe adequately the influence of the selected variables concentration of HPMC and concentration of glycerol & PEG-400 on the responses under study. The desirability function led to the optimum values of the factors at which the produced film showed fast drug release and suitable mechanical properties. The film stored under normal room temperature for 10 days did not show any changes with respect to content uniformity, physical appearance, *in vitro* disintegration and folding endurance. While the same formulation was not stable at accelerate condition (75% RH and 40°C). Further there is a need to cheque the stability for long period of time (2 – 3 years) for their suitability.

Keywords: HPMC, Solvent casting method, Fast drug release

ARTICLE INFO

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1. Introduction

Impotence: Impotence are mainly occurs by two way, primary impotence, and secondary impotence.

Type of impotence:

Endocrine or hormonal:

This occurs when there is an imbalance or insufficiency of sex hormones in the blood stream. It accounts for about 5 to 10 per cent of all organic impotence. Generally, hormonal changes affect the libido (or sex drive) rather than the quality of the erection per se. A variety of disease conditions can cause these changes. [1]

Mixed:

Sometimes, more than one factor can be operative in the same patient. Such patients generally have systemic disease. Notable examples are diabetes, kidney failure and liver failure. Another group where mixed factors operate is where long standing impotence has led to secondary psychiatric disorders such as depression etc.

Psychogenic:

When there is no organic factor and the problem lies purely in the mind, it is labeled a case of psychogenic impotence. But before such hasty labeling it is necessary to prove by andrological investigation that no organic or bodily cause exists. Only then can treatment proceed in a scientific and systematic manner. There are several treatment options for impotence. This is a very brief discussion on some of the options. [2]

Current treatment for impotence:

Conceling of sex:

Counceling and sex therapy are sometimes effective in helping patients with minor sexual problems, especially when these are caused by sexual ignorance and psychological factors.

Oral medication:

The introduction of Viagra by Pfizer in March, 1998,, marked the beginning of a revolution in the oral medical management of erectile dysfunction (ED, impotence). The launch of Viagra was soon followed by that of Levitra and Cialis. Other (even better) drugs are in the pipeline. Effective oral medication has re-written the management of ED and is effective in nearly 70 - 75 % of cases. [3,4]

Hormonal Replacement therapy:

Testosterone is the major male hormone that gives men their sexual characteristics (deep voice, beard, chest hair). As men age, their level of testosterone decreases (andropause) and this may have an adverse effect on sexual performance. In proven cases of andropause, testosterone preparations may enhance potency and improve sex drive. However, this therapy must be only offered under expert medical supervision because many side effects can occur. Other endocrine disorders causing low testosterone, elevated prolactin, and other abnormal hormonal states, will require specialist endocrinologist attention. [4-6]

External devices:

Vacuum therapy involves the use of an external vacuum device, and one or more tension rings. This therapy is purported to be effective for over 90% of the men who use it. In fact, most can technically master its use in one day, and can use it to maintain erections for up to 30 minutes, even after ejaculation and/or orgasm. Side effects, include

petechiae (reddish, pinpoint-size dots) and ecchymosed (bruising). These conditions are not painful or serious and generally occur only during an initial learning period. Penile temperature may decrease 1-2 degrees during use. Vacuum devices are generally favoured by elderly patients with erectile dysfunction. [5-9]

Panile injection:

Men must first be taught the procedure in the physician's office. These drugs produce erections of good quality for about 75-85% of patients who select this option. Some patients combine this method with the use of an external vacuum device. Not too many injections are used nowadays. Erections obtained by injection usually last 30-60 minutes and may not subside when a man has an orgasm or ejaculates, and may interfere with the patient's social/business agenda. An overdose can cause a prolonged and painful erection that may require medical or surgical intervention. Frequent use may lead to the build-up of scar tissue in the penis, further complicating the process of erection. [10-22]

Panile Implant: A penile prosthesis (implant) is a fixed or mechanical device surgically implanted within the two corpora cavernosa of the penis, allowing erection as often as desired.

Fast dissolving film: Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. (FDF) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to FDF formats. Today, FDF are a proven and accepted technology for the systemic delivery of APIs for over-the-counter FDF medications and are in the early- to mid-development stages for prescription drugs [23-26].

2. Classification of Oral Film

There are three different subtypes Flash release, Mucoadhesive melt-away wafer, mucoadhesive sustained-release wafers. These three types of oral films are differentiated from each other in following table.

Advantages of Oral Thin Film:

This dosage form enjoys some distinct advantages over other oral formulations such as.

Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity. The disadvantage of most ODT is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.

- As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
- Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter into the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect^[26]. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
- Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
- OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs. The formulation of dissolvable films are customarily facilitated through aqueous polymer matrices that span a wide molecular weight (MW) range, thereby providing flexibility to achieve certain physical properties.

Disadvantage of Oral Strip

- The disadvantage of OS is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip [27].
- There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose up to 30 mg. This clearly limits the range of compatible drug products.
- The other technical challenge with these dosage forms is achieving Dose Uniformity [22].

3. Application of Oral Strip in Drug Delivery

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. Dissolvable oral thin films (OTFs) evolved over the past few years from the confection and oral care markets in the

form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Application of FDFs are shown in figure.1.

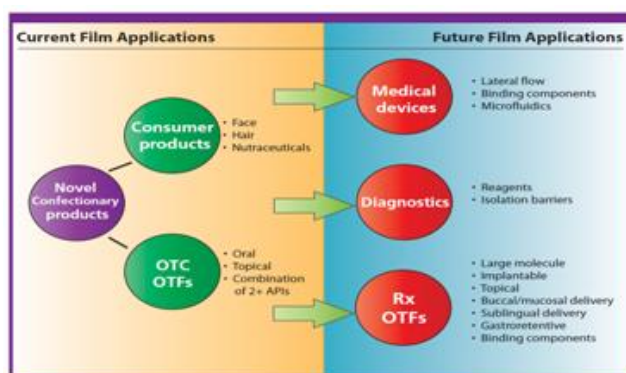


Figure 1: Application of FDFs

Present Work:

Objective of work: film was produce by solvent casting method

The film evaluated for following paramater.

Measurement of Mechanical property

In-vitro DT Time

Drug excipient study

Materials

Drug and Other materials like HPMC (E5, E6, E15 E55) povidon, pactin, Carrageenan, (EC) ethyl cellulose, poly caprolactum (PCL), dextran-T, guar gum, xanthan gum, carboxy methyl cellulose (CMC), micro crystalline cellulose (MCC), glycerol (G-ol), citric acid(CA) Sodium saccharin, Citric acid, PEG-400 (P-400), Sorbitol, Tween-80 (T-80), Sorbitol (S-ol) etc. used were of pharmacopeial grade.

Methods

The film forming polymer was dissolved in ethanol (EtOH) and other ingredients were dissolved in methanol (MeOH). Pour the ingredients solution drop by drop in previously prepared film forming solution with constant stirring to form clear solution. The solution was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass petridish having area of 76 cm² and was dried at room temperature. The petridishes were put on the leveled surface during drying to avoid variation in the thickness. The film took approximately 24 hours to dry at room temperature. The dried film was carefully removed from the mould and was cut into size required for testing. All batches contain 100 mg of sildenafil citrate which is equivalent to 8 mg SC per film of 2×2 cm² area for preparation.

Different polymer based comparative trial: In first batch, sixteen formulations were prepared by using glycerol and PEG 400 as a plastisizer in a fixed quantity with different polymer.

Compatibility of polymer & plasticizer with sildenafil citrate: Second batch, seven formulations of FDF were

prepared using fixed quantity of ingredients & different concentration.

Optimisation of concentration of selected polymer: Third batch, twelve formulation of FDF were prepared using fixed quantity of ingredients & different concentration of selected polymer.

Evaluation of Fast Dissolving Film:

Fast dissolving film should be stiff, flat and should not curl on the edges. The fast dissolving film strip must be robust enough to be removed from the unit-dose packaging and to be handled by the consumer without breaking. The film must also dissolve readily in order to deliver the active agent rapidly when placed in the oral cavity. Mechanical property of fast dissolving film plays an important role in deciding the formulations. [28-30]

4. Physical parameters

Morphology study:

Morphological study providing information regarding surface study of (FDF). Morphology study of FDF was carried out by Compound microscope.

Measurement of in vitro disintegration / dissolution:

In-vitro Disintegration study: The in vitro dissolving time was measured (n=3) for film of each batch in 20 ml of simulated saliva at pH 6.8 in glass Petridis. Film sample (2 cm x 2 cm) was placed in 20 ml of simulated saliva. The medium was kept mildly agitated using a magnetic stirrer. The time for complete dissolution of the film was recorded as dissolving time. The average of three measurements was taken into consideration.

In-vitro dissolution:

The dissolution study was carried out using USP paddle apparatus, at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using 300 ml of simulated saliva at pH 6.8 as dissolution medium. The agitation rate of paddle was 50 rpm. An equal volume of the fresh dissolution media, maintained at the same temperature was added after withdrawing the sample to maintain the volume. Then the solution samples were analyzed in UV-VIS double beam spectrophotometer (Sytronics UV-VIS spectrophotometer 118) while replacing the dissolution media as a blank.

Stability testing:

Films of optimized batches were subjected to stability study. Each film was wrapped in a butter paper and placed in plastic zip bag. Films were exposed to 75% humidity, 40°C temperature and ordinary room temperature. The study was carried out for 10 days. The films were evaluated initially and every 10 days for their physical characteristics, in vitro Disintegration, drug content uniformity and folding endurance.

Drug excipients compatibility study:

FTIR Study:

The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch were measured using Fourier Transform Infrared Spectrophotometer. The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400cm^{-1} .

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Evelution of Physical Parameter for FDF:

The visual identity overall elegance consumers acceptability, control or uniformity monitoring and trouble face manufacturing and reflecting of the general appearance of a FDF. The control or physical appearance of FDF involve 5ml measurement of a number of attributes such as thickness, shapes, presence or absence of an odor, taste, visual appearance color, consistency and identification marking. [31-32].

Preliminary studies were carried out to select a suitable polymer system and to obtain a good polymer plasticizer system, which is capable of producing films of desirable mechanical property and dissolution characteristics. Results were shows that formulations P1-4 produced good film as compare to others. All films as whole unit were easily peel able from glass Petridis without breaking film, so separability from Petridis is also not issue in all film formulation those prepared from HPMC. Physical appearances provided by these films gives appreciable result then others. All films prepared with HPMC had very nice clarity and transparency, without any grittiness.

Morphology:

This was supported by microscopic study results of the film, there were no any transverse scratches on the film . There were slight whitish small particle like image which may be drug or any another excipients that was recrystallized in minute amount but that was not seen by human eyes as such, so no more problem of patient incomppliance.

Measurement of In-Vitro Disintegration, Dissolution and Drug Content:

In -vitro disintegration and dissolution:

In vitro disintegration study is main key parameter to determine the amount of drug release in shorter period of time and simultaneously faster onset of action. Results shown in below table indicate that as the amount of polymer increase, in vitro disintegration study time increased proportionally since thickness of film increased as shown below.

Content uniformity:

Content uniformity is also important consideration in administering the precise dose in patient and thus content uniformity were evaluated for all factorial design batches and results are shown in table .Content uniformity is solely dependent on the manufacturing process. Results indicate that all batches had content uniformity more than 90% which was non problematic in case of sildenafil citrate. There were no significant changes observed for content uniformity with respect to polymer and plasticizer concentration in these experiments. HPMC polymer containing film are not showan disintegration & dissolution.

Drug realise study:

Have aresult basis dissolution profile various formulation was almost compltely relese from all the formulation within 5 minutes. Various durg realeased from FDF with different polymer & different concerntration for different formulation.

Drug Exipents Compatibility Study:

Furrier transfer infrared (FT-IR) Study:

FTIR spectroscopy was used as mean of studying drug excipients compatibility. The FTIR of pure drug and optimized batch formulations were scanned over a wave number range of 4000 to 400 cm^{-1} . In IR Spectrum of pure sildenafil citrate showed the presence of peak at 3458 cm^{-1} (NH stretching), 3298 cm^{-1} (OH stretching), ~1650, ~1590 cm^{-1} (C=N stretching), ~1690 cm^{-1} (C=O stretching of amide), ~1710 cm^{-1} (C=O stretching of citrate) group were characteristic of pure drug and all of them remain unaltered in IR spectrum of formulations, which indicate no drug excipients interactions.

Result:

The tablet is the most widely utilised oral dose format. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the ODT. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. A

number of ODT are commercially available for human use using technologies developed by pharmaceutical companies such as Cardinal Healthcare, Janssen. Pharmaceutical, Bioavail, and Eurand, Yamanouchi. However, these technologies use either expensive processing technology producing fragile tablets that require costly specialised packaging or use conventional tableting procedures which give longer than desired disintegration & still require specialised packaging. Dr. Zeibun Ramtoola and her team. The oral drug delivery market was estimated to be worth \$35bn in 2006 & forecast to reach \$52bn by 2010 with a CAGR of 10%. Of this, the ODT, taste masked & micro emulsion formulation segments constitute a 22% share with an expected CAGR of 17% to 2010. With multiple new consumer health and prescription product launches in recent years, the ODT market was predicted to easily reach \$3 billion in 2006, including brands and generics. The market continues to grow 20% each year, with a growing penetration of generic ODTs.

Table 1: Classification and Common Causes of Erectile Dysfunction

Category of ED	Common disorders	Pathophysiology
Neurogenic	Stroke or Alzheimer's disease Spinal cord injury Radical pelvic surgeries Diabetic neuropathy Pelvic injury	Interrupted neuronal transmission Failure to initiate nerve impulse
Psychogenic/psychogenic	Depression Psychological stress Performance anxiety Relationship problems	Impaired nitric oxide (NO) release Over-inhibition of NO release Loss of libido
Hormonal	Hypogonadism Hyperprolactinemia	Loss of libido Inadequate NO release
Vasculogenic (arterial and cavernosal)	Hypertension Atherosclerosis Diabetes mellitus Trauma/ Bicycling accident Peyronie's disease	Impaired veno-occlusion Inadequate arterial inflow
Drug-induced	Antihypertensives Antiandrogen Antidepressants Alcohol abuse Cigarette smoking	Central suppression Decreased libido Alcoholic neuropathy Vascular
Systemic diseases	Old age Diabetes mellitus Chronic renal failure Coronary heart disease	Multifactorial Neuronal and vascular dysfunction

Figure 2: Classification of Oral Film

Subtype Property	Flash release wafer	Mucoadhesive melt-away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4

Thickness(μm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer System	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue (upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

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