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ORAL FILMS: EXPANDING THE ORAL DELIVERY TECHNIQUE, BASICS, CHALLENGES AND CURRENT TRENDS

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ABSTRACT

Much interest has been indicated in non-invasive drug delivery strategies that achieve fast onset of drug action, prevent its rapid degradation but enhance targeted release. In recent times, the oral film technology has received much attention in line with this because of its versatility, availability for incorporation of numerous drugs as well as its usefulness to deliver therapeutic agents in paediatrics, geriatrics, dysphagic patients, and the bedridden, giving it an edge over similar oral solid dosage forms. Where interest in technology is great, constant research and development will be on, with resultant avalanche of insight on the subject. Since early 2000s, several research works have been published in scientific journals on design and formulation of possible drugs as oral films, usable polymers for films formation, drug-polymer compatibility, and evaluation techniques for them. These positive developments present numerous possibilities, while not without the challenges amidst. This has prompted the need for an up-to-date literature on information available on oral films technology. This review describes the fundamentals of oral films, covering their classification, current methods of manufacture, and oral films available in the market. It spirals into conclusion highlighting the untapped possibilities associated with this delivery system as well as the recent applications of nanosized drug carriers and proteinous drugs in oral films while not ignoring inherent challenges amidst the positives**.**

KEYWORDS: Oral films, proteinous products, nanoparticles.

1.0 INTRODUCTION

Work in progress! This succinct expression describes a fact at all levels of life, whether microscopic or macroscopic. Just as microorganisms keep working to proliferate, so are researchers to combat the havoc of drug resistance by harmful microbes, discovering new drug molecules having better therapeutic potency but fewer side effects and formulating innovative drug delivery systems. Drug delivery systems are formulation techniques or strategies aimed at drug transportation to intended site of action in the body. Such techniques provide protection to the drug during the movement but release them at the needed site of action, even at predetermined rates. Of several delivery systems, solid dosage forms have had the greatest patronage owing to available technology, stability, ease of administration and transportation, and high level patient compliance.[1], [2]

Caplets, capsules, softlets, and tablets (whether dispersible, soluble, chewable or modified release forms) are all examples of solid dosage forms that have been developed as a result of work of research in oral solid drug delivery. Solid dosage forms for oral use require swallowing for the drug release to begin. However not all patients can easily swallow! The problems of dysphagia, bedridden patients, and fear of choking, trendiness, flexibility and need for adjuncts for administration and the reducing effect of the first pass effect are set backs to total acceptance of oral solid dosage forms. Oral film, nevertheless, has been a revolutionary solid delivery system that has come to the fore in circumventing some of these challenges. This delivery system is one of choice for patients with difficulty in swallowing, the bedridden, those with repeated emesis, motion sickness or with mental disorders.[3]

Oral films, fast dissolving oral films, oral strips, oro-mucosal films or oro-dispersible films are all different nomenclatures describing one and the same delivery system. The Food and Drug Administration of the United States (FDA) even uses the term oral soluble film. They are therapeutic delivery systems usually made of hydrophilic polymers supplying active pharmaceutical ingredients (or pharmaceutical actives) after oral administration using oral, buccal, sublingual, palatal, or gastrointestinal absorption.[4] No doubt much work has been done and progress is being recorded in the formulation and development of many drugs as oral films. This is not without challenges that require overcoming, using available potentials to the full. Several works have been published since the last decade on formulating and evaluation of oral films of different medicinal agents, hence the need to bring readers and researchers up-to-speed with recent advances and applications of oral films by scientists in

this sphere, becomes pertinent and has informed this review. The review covers the basics of the oral film delivery system, pointing out progress, challenges and potentials associated with oral films while presenting current introduction of nanomaterials and proteinous therapeutic agents in oral film delivery system.

1.1 Historical Overview

Although there have been films as pharmaceutical dosage forms for topical (transdermal and vaginal) delivery, oral films were developed and found in patent literature in the 1960s as a novel drug delivery system but has now generated much interest over time because of its route of administration, versatility in classes of drugs delivered as well as the categories of patients targeted.[5] Oral films reportedly came into the market mainly as mouth-freshening consumable products with ingredients such as menthol and thymol as seen in products from Johnson & Johnson in the United States and Europe; Boots (Nottingham) in the United Kingdom, whereas Pfizer (New York) introduced Listerine Pocketpak strips in 2001. The oral film was now seen with the potential to deliver drugs to bed-ridden patients and those with dysphagia; overcoming tablet choking that is common with paediatrics and geriatrics. This heightened the popularity of oral films.[6], [7] Thus Chloraseptic® relief strips of 7-benzocaine was launched by Innozen (Oxnnard) as the first over-the-counter oral films with therapeutic indication to treat sore throat**;** others.

Table 1: Overview of this article.

Highlights
Introduction
Historical overview
Oral film Classification
Mechanism of drug uptake
Film manufacturing techniques
Film evaluation and Quality control
Packaging principles and challenges of oral films
New concepts of drug incorporation into oral films
Conclusions

Such as Sudafed PE(Phenylephrine/Triaminic) Quick Dissolving Films®, Simethicone oral films called Gas X Strips® (Norvatis consumer health**)** came into the drug market and now VitB_{12} oral strip as well as octane boost energy strip® of 40mg caffeine both by ODF Pharma (Quebec, Canada) are available. So to achieve different functionality of the oral film, several film formulations have been made, and many Pharmaceutical companies have had to tap into

the commercial viability of oral films technology to achieve higher market quote because a prescription of oral film prescribed would hardly be substituted with a tablet or capsule.[8]

Several oral films ranging from those of over-the-counter (OTC) drugs to prescription ones have become available in the market in different parts of the world. Such films now marketed possess different unique properties and this necessitates oral film classification.

1.2 Oral films Classification

While many users hardly prolong their stressful day by the technicalities of oral film classification, Srinivasan 2016 had attempted to classify Oral films on the basis of three unique criteria; (a) onset of release of active drug (b) site of application and absorption or (c) solubility of the active ingredient within the film and after release.[4]

(a) *Onset of drug release*: Using the time of release of active drug, oral films could be broadly grouped into three: *The Flash release*, which lets out active ingredient within seconds of administration to trigger a local or systemic effect. It is usually made of a single layer and is similar, in principle, to immediate release tablets. *The Mucoadhesive melt release* oral films disintegrate in minutes, forming gels and releasing their drug content to exert effect. They could be single or multi-layered oral films and on administration attaches mainly to the gingival or buccal region of the oral cavity. And the third is *The Mucoadhesive sustained release system*. This multi-layered film delivery system dissolves between 8-10 hours to disperse drugs for systemic or local effect. It gets attached to a site of the mucosal membrane in the mouth. It could be seen then that both mucoadhesive melt and mucoadhesive sustained release film delivery systems are modified release systems.[3]

(b) The solubility of the active drug: This is important to oral film classification. The active ingredients are dissolved in the film polymer or dispersed within it. Also as the active ingredient is released, these could become dissolved in the surrounding aqueous saliva medium, or dispersed in the medium for drugs not soluble. Films with drugs soluble in the polymer or aqueous medium are named oral dissolving films. These films usually contain class I and III drugs of the biopharmaceutical classification system (BCS) that meet other needed requirement for the oral film production and are targeted for absorption in the mouth.[9] However films with drugs that are not soluble in aqueous polymer solution are dispersed in the films. They mainly contain drug actives from classes II and IV of the BCS which have poor aqueous solubility. They are appropriately termed oral dispersible films.

Although these two terms for oral films are being used interchangeably likely unknowingly or unconsciously, the classifications help for clarity, setting records straight and ensure accuracy of information.

(c) ***Site/route of administration;*** On the basis of site of administration and uptake of ingredient, oral films could be termed as palatal films (when applied on the palate), sublingual films (for those placed under the tongue), gingival films for those stuck to the gingiva or buccal films, for the ones attached to the inner cheek.

1.3 Mechanism of uptake of drug content from films

Apart from parenteral route, drug uptake from all other route of administration involves absorption; that is the movement of substances from the point of administration into systemic circulation through the epithelium or endothelium. Drug release from oral films is thus transferred from site of administration into systemic circulation. In line with the modified Fick's first law of diffusion, drug absorption is indirectly proportional to thickness of the oral film and that of the oral mucosa layer. Such thickness implies drugs navigating through several layers within the films and the oral mucosa before getting to the desired systemic circulation. Parts of the oral mucosa responsible include the sublingual (under the tongue), buccal (inside the cheeks), gingival (the gums) or the palates. The high permeability and rich blood supply of the sublingual route affords it to achieve rapid onset of action and high bioavailability so the drug with short delivery period can be delivered.[10] The rate and extent of absorption of the drug follows the order; Sublingual > Buccal > Gingival >Palatal. After the drug penetrates the oral mucosa, it is absorbed into the reticulated and jugular veins and then drained into the systemic circulation. This circumvents hepatic first-pass metabolism.[11] Therefore, this route of administration may improve bioavailability, reducing associated untoward effects. Drug absorption through the cells in the oral mucosa as other part can either be transcellular (across) or between cells (paracellular). Transcellular absorption is associated with drugs having poor aqueous solubility as they take advantage of the lipid bilayer of the cell membranes, whereas the more hydrophilic ones are absorbed via the route between the cells, but usually both routes are possible.[12]

1.4 Oral films: Advantages and Limitations

Since oral films are placed on the tongue where they dissolve or disperse rapidly in the saliva, oral film is not expected to be swallowed wholly. This property makes them particularly suitable for patients with dysphagia, Parkinson's diseases, mucositis or emesis, whether they

are paediatric, geriatric or bedridden patients.[13], [14] Oral films attain rapid wetting, may adhere to the buccal mucosa, so that it is less likely to be spat out. Interestingly, unlike other oral deliveries such as tablets and capsules that require adjuncts, such as water for administration, oral films need no adjunct hence are ideal for patients or travellers even with no access to water. Also, to achieve fast disintegration during production of oral dispersible tablets, mechanical robustness may at times be secondary, but oral films combine mechanical integrity, robustness and rapid disintegration, giving it an edge over other similar solid oral dosage forms.[14] Its rapid disintegration time of few seconds and mucosal absorption brings about rapid onset of action and avoidance of hepatic first pass, ensuring better bioavailability. Nevertheless, rapid onset of action of films can be of advantage when they contain antiallergics and other emergency drugs (eg loratadine, diazepam), or rapid pain relief but might be a disadvantage in drugs with adverse effects that can induce sedation (eg chlorpheniramine).

The limit to drug loading capacity, taste of therapeutic active and harsh manufacturing conditions to some active ingredients and excipients are some challenging setbacks readily identifiable in oral films production. Since there is a limit to drug load unto films, not all active principles can be delivered as oral films except the highly potent, low-dose drugs. Even the incorporation of more than one drug concomitantly is a task quite challenging in oral film formulation because both the dissolution rate and disintegration time can be affected negatively by such co-administration of drugs in oral films.[15] Manufacturing of oral films may require use of solvent and heat application, especially during drying. These conditions could be harsh, denature thermolabile drugs and excipients or chemically modify them by hydrolysis. Interestingly too, the long duration of stay of oral films in the buccal cavity, particularly on the tongue, could make taste-masking very difficult for an active ingredient with extremely unpleasant taste. And if taste-masking is achieved, it may even require large amount of flavouring and sweetening agent used and can further reduce the permissible dose of the active ingredients that could be loaded. Achieving dosage uniformity of oral films can also be a challenge depending on the method of production of the oral film.

[16], [17]**Fig. 1: Examples of oral films in their trendy packages as obtainable in the market.**

2.0 Oral Film Manufacture

2.1 Production processes of Oral films

The process of manufacture of oral films could be broadly divided into four;

1.) The Casting and Drying method

2.) The Extrusion method

3.) The Rolling method

4.) The Printing and spraying methods

The Casting and drying method could be subdivided into the solvent casting method, the semi-solid casting method and the freeze dried method.

(i) Solvent-casting/solvent evaporation method: Oral films are preferably formulated using the solvent-casting method, whereby the water-soluble film forming polymer is dissolved to form a clear, viscous solution. The active drug and the other excipients are dissolved in another solvent, then combined with the bulk viscous solution. Any air entrapped in the viscous solution during mixing is removed by vacuum to obtain film with uniform thickness. The resulting solution is poured into plates, and the solvent evaporated to dryness in an oven, and formed films cut into pieces as desired. Solvent selection for the solution to be casted depends on the physicochemical properties of the drug. These properties include drug compatibility with film-forming excipients, solvents, and temperature sensitivity. Moisture and temperature affect this process. Moisture influences stability and mechanical properties of formed films significantly while controlled temperature condition is necessary to maintain the viscosity of the solution and thermo-sensitivity of the active drug.[18]

In large scale production, specific types of equipment such as rollers are required for pouring the mixed solution of drug and polymer on an inert base which is usually, glass, plastic, or teflon plates. The clearance or space between the roller and the base determines the thickness of the film. As the film dries, the solvent is removed and helps to obtain the finished product.

Some problems possibly encountered when the manufacturing technology is scaled-up from laboratory to production scale have been reported in literature[7] can include the casting of the film, obtaining uniformity in thickness, and selection of proper dryer to obtain quality finished product. Dried films are cut, striped, and packaging done. Suitable sizes and shapes of films commonly available are 3×2 cm^2, 2×2 cm^2 or 1.5×2.5cm^2.

(ii) ***Freeze drying method*****;** The method of preparation is similar to that of the solvent casting but differs at the level of drying. Here the freeze-dryer is used to eliminate the solvent. Shamma and Elkasabgy had prepared spironolactone oral film using this method whereby the dispersion was initially frozen at -20^{o}C and the pressure of the condenser chamber kept at 7×10^{-2} mbar while the temperature was at -50^{o}C. This is particularly valuable for products that are heat-sensitive and may denature or become modified when use of heat is employed. It has been reported that the properties of films produced using freeze drying methods are unique when observed under electron microscope.[19]

(iii) ***Semisolid casting*****:** In the semisolid-casting method, two separate solutions are prepared. First is a solution of the film-forming polymer. The next is an alkaline solution of polymer that would be insoluble in an acid (e.g., cellulose acetate phthalate and cellulose acetate butyrate). The latter solution is added to the previous together with incorporation of a plasticizer to obtain a gel mass. The gel mass is cast into moulds and dried at controlled temperature.[7]

Printing method; Although the concept of printing on paper and other items and especially in pharmaceutical industry are not in themselves new, its application to film manufacture is. Labels on pharmaceutical preparations are products of printing, tablets are embossed or debossed (a form of printing) with unique features during production for the purpose of identification, and prevent counterfeiting. 3-D printing use in production of oral films is, however, a recent development used to incorporate therapeutic agents prone to denature due to heat. In formulating films of such agents any heat related manufacturing process would be avoided. Proteins and peptide molecules have been reportedly produced as oral films by these

methods.[8] Of the printing technologies, two types have been mentioned in literature; the ink-jet method and the Flexographic printing technologies (FPT).[20] The inkjet printing was used for printing of drug on different polymeric substrate, whereas the flexographic printing was employed to coat the drug loaded substrate with a polymeric thin film. Both types use similar principle of incorporation of drug unto an already formed oral film from the polymer.[21] Specifically, a film excipient is mixed and formed before incorporation of the drug by imprinting. By this method, the biostructure of a protein drug, which can be affected by mechanical stress, dehydration, and heat resulting in loss of activity, remains unchanged. The main difference however between the two printing process is in the principle of imprinting. Whereas FPT introduces the drugs posteriorly using rotating rollers, the inkjet incorporates the drugs as drops through an outlet on the inkjet. Moreso, inkjet printing would not be ideal for drugs subject to hydrolytic degradation.[8] Thus one unique potential in printing method of oral film manufacture is that of medicine and dose individualization.[20] A patient's customized medicine could be imprinted on an already prepared polymeric substrate at the point of collection.

Spraying method

Spraying of a drug-loaded solution or suspension onto a plane carrier could be another alternative for film manufacture. This method of oral film manufacture especially for multilayer film has been described in the patent literature where in one layer is produced, for example, by solvent casting method; the second layer is sprayed onto the first as suspension or by electrically charging a powder mixture including the drug.[22] This is an open opportunity for production of modified release oral film.

The Extrusion technique; the extrusion method involves forcing a mixture of film components through an orifice (die) using an extruder. It is a process that has been used for other solid dosage forms, although its reported use in oral film formation is limited.[23] It is divided into two;

(i) Hot-melt extrusion (HME). HME has been used to prepare several delivery systems: granules, sustained-release tablets, and transdermal delivery systems. Its principles are adopted from the plastic manufacturing industry. In the oral film manufacture components such as drug combinations, polymers, and plasticizers are extruded into various final forms to achieve desired drug-release profiles.[24] The heat process and absence of solvent makes it unique. The API and other excipients are mixed in a dry state, heat applied, through the

heaters of the extruder, to form a molten mass which is extruded (forced-out) through the orifice. The films are allowed to cool and are cut to the desired size. Hoffmann had described the application of this technique in sustained release oral film though challenge of the film thickness and disintegration persists.[14] However, the HME process is associated with the following setback; its suitability for only thermo-stable drugs and difficulty in sourcing for film forming polymer that can withstand the heat.[7]

***(ii) Solid-dispersion extrusion*.** The term solid dispersion describes the distribution of one or more solid (eg therapeutic actives or drug) within another solid, the inert carrier (eg amorphous hydrophilic polymer) using methods such as HME. The drug is initially dissolved in a suitable liquid solvent to form a solution. Then the solution is incorporated, without removing the liquid solvent, into the melt of polyols eg polyethylene glycol. The selected solvent or dissolved drug may not be miscible with the melted polyethylene glycol. As this cools, solid dispersion forms and the immiscible components with drug are extruded through dies that determines the film shape. The liquid solvent used could affect the polymorphic form of the drug precipitated in the solid dispersion.[25], [7]

Rolling method: In the rolling method, a viscous mix of the drug is rolled onto a carrier.[14] A solution of the drug is formed, the solvent being mainly water or alcohol-water mix. A premix (or master batch) is prepared containing the film-forming polymer, polar solvent, and other excipients, except the drug. A predetermined quantity of the master batch is fed through a metering pump and control valve to mixers while the required amount of the drug is also added to the mixer through an opening. Blending of the drug and the master batch provides a uniform viscous matrix that is fed to the pan using metering pumps. The film is dried on the rollers, and then cut into desired size and shape. The thickness of the film is controlled using a metering roller. The film is thus a product of a uniform blend of the drug and the premix. The drying of the film is under controlled condition, to avoid external air currents or heat on film surface.[7]

2.2 Packaging. Since the stability of oral films is affected by moisture and temperature, selection of an appropriate primary packaging container is an important decision for manufacturers of oral films. The packaging container should provide sufficient mechanical protection to the film from external factors such as mechanical abrasions, impacts, light, temperature and humidity either during storage or transportation. Aluminium foil, paper or plastic pouches or combinations of them have been used for packing oral films.[20] These

packaging materials are easy to handle, not expensive and easily formed as flexible pouches by vertical or horizontal forming method during product filling.[26] Both multi-dose and single-dose packaging are possible depending on the film characteristics, but single packages are preferred because film sticking and resultant overdose is avoided. A single dose sachet, Pocketpaks™ produced by Pfizer contains Listerine. A single dose of desired size is cut from a continuous film produced from a roll dispenser (each size equalling individual dose in single packages). Any inspection on such system of continuous production is done by automatic in-line in-process control. But at specific intervals, weight uniformity of each is checked off-line. To meet industry regulations on identification to reduce counterfeiting, necessary information can be printed directly onto the film before packaging.[27] Formulated films in primary packages are to be inspected thoroughly before being put into secondary packaging container. One potential in films packaging is the recent innovative packaging technology the Rapidcard (Labtec APR) for Rapid® film now in use. Rapid card comes in the size of a bank credit card but has 3 removable films takeaway medicine that is trendy.[28], [14] Thus innovative packages that are child-resistant and geriatric-friendly are suitable.

Table 2: Some active drugs formed as oral films.

Indications	Active drug	Film forming polymer	Reference
Allergy	Chlorpheniramine	Enterolobium gum; Cassava starch	[29] [30]
Hyprtension	Amlodipine	Bean starch and HPMC blends	[31]
Algesia	Tramadol	PVP and Chitosan	[32]
Hypertension	Propranolol HCl	HPMC/Polycarbophil	[33]
Hypertension and angina	Carvedilol	Chitosan and pectin	[34]
Asthma	Salbutamol sulphate	Eudragit, PVA, Carbopol and Hpmc blends	[35]
Nausea and vomiting	Domperidone nanoparticles	HPMC	[36]
Oral candidiasis	Miconazole	Sodium alginate or pullulan	[37]
Nausea and Emesis	Domperidone	Polyvinyl alcohol (PVA)	[38]
Ulcer	Omeprazole, Rabeprazole	Sodium alginate HPMC and PVP	[39] [40]
Insomnia	Zolpidem nanospheres	Blend of HPMC Eudragit RL and Carbopol	[41]

2.3 Typical Composition of oral films

Similar to other dosage forms with their additives, the composition of oral films are basically the drug and the film forming polymer. Other excipients such as plasticizers, surfactants, colorants, saliva stimulating agent, flavouring agents, are included depending on the intent of the formulator, properties of the drug and the level of compliance by the patient desired.

Drug: Although several therapeutic actives can be presented as oral films, not all drugs are suitable or could be delivered as such. Table 2 presents drugs that have been delivered as oral films. The choice of active ingredient is not a blind or haphazard guess selection but is based on drugs meeting specific criteria. Drug taste and solubility are some properties to watch out for during selection but these could be overcome by use of sweetening agents and dispersion techniques. Micronization, a means to achieve better dissolution or dispersion can also help to attain dose uniformity and reproducibility in the films. The main restrictions to selected drugs are high dosage and high molecular weights which makes them difficult to be loaded since only 5-30% w/w of the film is usually composed of the active drug.[42] Norvatis' 62.5mg of Simethicone per strip is the highest dose loaded oral film followed by the 50mg diclofenac film by.[43] Stability of the drug in saliva is equally important in drug selection for oral film to prevent activity loss due to hydrolysis.

Table 3: Some class of drugs that can be formulated as oral films based on their dose.

Class of Drugs	Possible members that can be formed as oral films
Phosphodiesterase 5(PDE_5) Inhibitors(drugs for Erectile dysfunction)	Sidenafil, Tadalafil
Antihyprtensives	Amlodipine, Nifedipine, S-amlodipine
Antiallergics	Loratadine, Diphenhydramine, Cetirizine, Desloratadine
Statins for dislipidaemia	Simvastatin, Rosusvastatin, Fluvastatin
Anti-epileptics and Sedatives	Bromazepam, Diazepam, Nitrazepam, Lamotrigine
Analgesics	Tramadol, Naproxen, Diclofenac
Vitamins and Hormones	Ascorbic acid (Vit C), Riboflavin (Vit B12), Melatonin
Anti-migraine	Sumatriptan, Zolpitriptan, Almotriptan
Antidepressants	Fluoxetine, Paroxetine, Sertraline
Anti-nauseating, anti-emetics agents	Domperidone, Metoclopramide, promethazine, Ondansetron
Proteins and peptides	Calcitonin, Buserelin peptide, Insulin
$5HT_3$ receptor antagonist	Ondasetron, granisetron

Other components of oral films are the excipients that help form the film and make them not only appealing but also palatable. These include:

Film forming polymers: These form the highest percentage of ingredients for manufacture of oral films, forming about 40- 50%w/w. They make film manufacture a possibility. The amount of the polymer added in the oral film determines how robust the films will be. For a polymer to be ideal for film formulation, its availability, non-toxicity, ready wetting or spreadability are desired properties. Also the polymer on forming films must peel from petri plates, have a good mouth feel and high tensile strength. Several classes of polymers have been used in film formation, varying from starches, gums, celluloses to their respective

modified derivatives. For oral films, water soluble polymers are usually employed because quick disintegration, good mouth feel, and mechanical properties are achievable with it.

Although each polymer has unique characteristics, a combination of two or more can give a film with improved properties or at least reduces cost. Ayorinde *et al.*, 2016 and Anoop *et al.*, 2013 have used polymeric blends in formulation of fast dissolving oral film and have reported on the advantages.[31] [44]

Plasticizer: The flexibility of oral films is due to presence of plasticizers in their formulation. Plasticizers act by influencing the glass transition temperature of the polymer, thereby improving its strip property. Commonly used plasticizers are poly hydric alcohols such as glycerol, propylene glycol, low molecular poly ethylene glycol; phthalates eg diethyl phthalates, dibutyl phthalates; citrates eg acetyl citrate, triethyl and tributyl citrates. Plasticizers improve flow of film forming polymers during preparation and also enhance strength of oral films formed.[45] At times, plasticizing effect are modified giving a better mechanical strength to films using combination of more than one plasticizer.[44] Nevertheless, wrong use of plasticizers, in terms of selection of incompatible ones or disproportionate quantity may lead to faulty films that could manifest as cracking, splitting or peeling of the films.

Penetration enhancers: A new class of ingredients incorporated into oral films because of their impact in films are the penetration enhancers. They act by promoting penetration of active drug moieties from the films into the oral tissues while not expected to cause any irritation in the tissues. The use of penetration enhancers has been common with dosage forms for tropical use. Water has been used as such to hydrate the skin thereby improving dermal permeation, to achieve transdermal delivery. However, its application in oral films is a welcome development in overcoming the challenge of drug permeation at site of administration. Among the chemicals with the property to cause enhanced tissue permeation are polar solvents (eg water, ethanol) surfactants (eg tweens) terpenes (eucalyptus) and bile salts. Chitosan and its thiolated form have also been reported to improve oral tissues penetration, especially as they are mucoadhesive.[42]

Surfactants: Beyond disrupting the surface of the oral epithelium for drug delivery, surfactants could be incorporated into films to act as solubilizing and wetting agents so that rapid dissolution or dispersibility of oral films in the oral cavity within the shortest timeis

achievable. The enhanced wetting results from the reduction (brought about by the surfactants) in the interfacial tension between the film and the aqueous medium of saliva. Tween 80, benzalkonium chloride, sodium lauryl sulphate and polaxamer 407 have been widely used.[46]

Colouring agent: For the purpose of imparting easy or unique identification, aesthetics or matching of flavour to appearance, colouring agents are added to oral films. Their concentrations usually do not exceed 1%w/w. Among the colouring agents in use mainly in oral films are silicon dioxide and titanium dioxide.[47]

Saliva stimulating agent: These agents cause increase in the production of saliva, providing the medium available for the disintegration of the oral films. Saliva stimulating agents include acids like citric acid, tartaric acid, ascorbic acid and malic acid. Their mechanism of action is likely due to their sour taste, thus triggering saliva production to dilute the sourness. These acids can be used alone as well as in combinations.

Sweetening/Flavouring agents: Sweeteners are vital ingredients in oral films because of the longer contact time of films on the taste-buds in the mouth hence need to mask drugs with unpleasant taste delivered as oral films. Natural sugars such as sucrose, glucose, maltose, xylose have been a good source of sweeteners, however their use is limited in diabetics and the obese. Artificial sweeteners such as Saccharin and aspartame (the first generation) or acesulfame-k, sucralose and neotame (the second generation) are used instead in such classes of patients.[48] Generally, in the concentration of 3 to 6%w/w, sweeteners are used either alone or in combination. Polyhydric alcohols such as sorbitol, mannitol and isomalt can equally be used alone or in combination as sweeteners with additional advantage of providing good mouth feel and appealing taste sensation.

About 10%w/w of the total weight of oral film is made of flavors which are added to the formulations.[49] While their functions are inter-related, flavors are not sweeteners. Sweeteners improve taste, whereas flavouring agents give aromatic appeal, palatability and acceptance to a preparation.[42] The acceptance of the oral film by an individual is largely dependent on the initial flavor quality obtainable in the first few seconds on administration and the residual taste of the formulation. Oral films for both paediatrics and geriatrics could be flavoured and the flavoring agents can be selected from synthetic flavor oils, oleo resins, and volatile oils from various parts of plants.

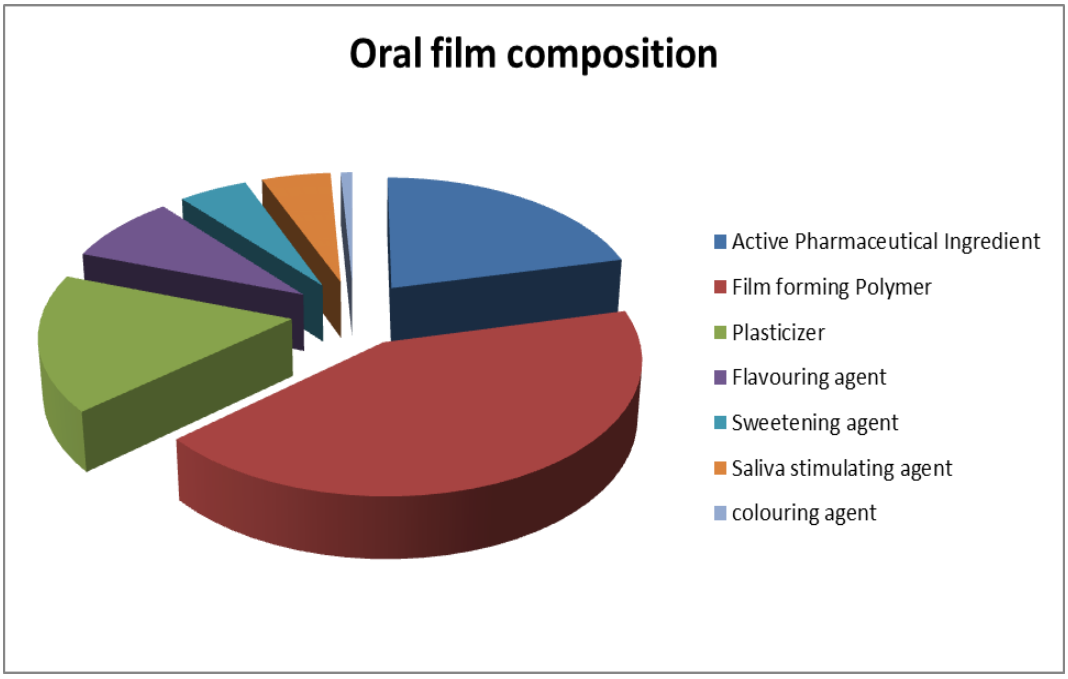

Fig. 2: Schematic representation of percentage composition of Oral films.

3.0 Quality Control: Evaluation of Oral films

3.1Organoleptic evaluation

***Taste evaluation*:** This is done to determine the acceptability of the taste and flavour of the film by the patients. This is important since oral films stay in the oral cavity for some time, sufficient for patients to detect the taste. Human volunteers are used for in-vivo taste screening especially for small sample size, but for the purpose of uniformity of assessment and avoidance of subjectivity of obtained results, an electronic 'tongue' having test sensors have been reportedly used to evaluate taste of oral film.[50] Such in-vitro method becomes especially appropriate in high throughput taste sensing of such dosage forms.[49], [7]

Physical appearance of Oral films

The oral film appearance can be evaluated visually or mechanically**.**

Visual inspection involves the use of the sense organ of sight. After preparation the film, it is usually observed for colour, homogeneity and transparency. Having a feel of the film also gives information on the surface texture. Other evaluation means for the appearance are.

Surface morphology of the oral films can be performed using the scanning-electron microscopy (SEM), electron photomicrography or optical microscopy methods. Any difference in the upper and lower surface of the film is watched out for. The uniformity of the

film and absence of pores or striations indicate the good quality. SEM images could be used to examine oral film surface to confirm the drug distribution within the film after incorporation.[46]

3.2 Mechanical properties of films

Tack test

How well an oral film adheres to a surface such as a piece of clean paper sheet when pressed into contact with it, is termed tackiness. The degree of stickiness or tackiness is a function of level of dryness of the film. There are eight stages of film drying process: set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through, dry-to-recoat and dry print-free.

***Tensile strength*:** It is a measure of the maximum stress applied at two points on the film at which the film breaks. To determine it the film is held between two clamps and pulled. The applied force and the increase in length of film are noted just at point breakage. It is given in the formula below:

$$Tensile\ strength = \frac{Force\ at\ film\ breaking\ point}{Area\ of\ film}$$

The tensile strength of an ideal oral film should be relatively high at breaking point and should have high percentage elongation value but a low elastic modulus.[40]

Percentage elongation: This parameter comes to bear when a force is applied to a film sample. The film sample stretches and the increase in length is referred to as strain while the applied load is called stress. Strain is basically the deformation of the film divided by the original dimension of the sample. Percentage elongation is expressed mathematically thus**;**

$$percentage\ elongation = \frac{increased\ length\ of\ film}{original\ length\ of\ film} \times 100$$

It has been reported that as the plasticizer content increases, film elongation is observed.[49]

Tear Resistance

The ultimate resistance to film breakage is the tear resistance thus since the actual force that oppose tear is equal to the Maximum force needed to cause the tear, the force required to cause film tear is then measured as tear resistance value. This test is typically developed from that used in the plastic industry. The rate of loading employed is 2 in/min which is to determine the magnitude of force required to start a tear in the film specimen. That value of

force necessary for tearing is generally found near the onset of tearing and is taken as tear resistance value.[48]

Folding Endurance Test

It is determined by repeatedly folding, randomly selected films at the same axis until the film breaks or develops visible cracks. This test is carried out under bright light so that any crack on folding is detected. The number of times the film is folded just before breaking is computed as the value of folding endurance.[30] This parameter gives information on brittleness of film or to what extent it could bend or be folded. Mechanical strength and folding endurance of films are related. As mechanical strength is improved by increasing plasticizer concentration, it is clearly evident that plasticizer concentration also indirectly affects folding endurance value.[48]

Moisture Uptake

The physical stability and integrity of oral films at high humid conditions is investigated using the moisture uptake test. To perform the test, an already weighed film is placed in the desiccator at room temperature, containing saturated solution of potassiun chloride, and the relative humidity inside the desiccator kept at 84%. After 3days, films are taken and weighed. The percentage moisture absorbed by the films is found using the equation.[42]

$$\%\ \boldsymbol{Moisture\ uptake} = \frac{\boldsymbol{Change\ in\ weight}}{\boldsymbol{original\ weight}} \times \mathbf{100}\ .$$

Elastic modulus Also called Young's modulus, is the measure of how stiff an oral film is. It is represented as the ratio of applied stress divided by the strain in the region of elastic deformation:

$$\boldsymbol{Young\ modulus} = \frac{\boldsymbol{slope}}{\boldsymbol{film\ thickness} \times \boldsymbol{crosshead\ speed}} \times \mathbf{100}$$

There is an interrelationship between tensile strength, young modulus and percentage elongation and it is that oral films that are hard and brittle have a high tensile strength and Young's modulus but less percentage elongation.

Swelling

To adhere to a biological surface and effect drug release, a polymer will need to swell. Film swelling studies can be conducted as reported by Arya 2012 using distilled water or simulated saliva solution as medium.[25] Each sample film is weighed and placed in a pre-weighed

stainless steel wire mesh then submerged into 15ml medium in a plastic container. The weight increase of the film is determined at definite time interval until a constant is achieved. The degree of swelling can be calculated using the formula below,

$$percentage\ swelling = \frac{increased\ weight\ of\ film\ at\ specific\ time}{original\ weight\ of\ film} \times 100$$

Percentage swelling measures polymer hydration giving information on relative interraction of the network structure of polymer matrix to movement of water molecule. In many cases the degree and rate of swelling play affect drug release. Hence, swelling rate and degree can be considered as the indicators for mucoadhesive potential and drug release profiles. For hydrophilic polymers depending on their number and strength of hydrogen bond they form in aqueous medium influence their network structure, on being hydrated and swollen become go into solution and is eroded.[34]

pH value

The pH value can be determined by dissolving one oral film in 10ml distilled water and determining the pH of the obtained solution. It is necessary that oral films have pH value near neutral so as not to be irritating to the oral mucosa.[29]

3.3 Drug excipient compatibility

Analysis of pure drug, excipient and their physical admixtures for any incompatibility or interraction is carried out using Fourier transform Infra-Red (FTIR) or differential scanning Calorimeter. The spectra or the thermogram are analysed to see any introduction of a new peak as a result of any incompatibility. The temperature range in the calorimeter is 25^{o}C-200^{o}C while the wave number range for the FTIR spectrophotometer is 400cm^{-1} – 1600cm^{-1}.[29]

3.4 Stability studies

The stability study on formulated films as reported in literature can be carried out for a period of 45days, 3months or 6months at conditions of 2-8^{o}C (45%Relative Humidity), 25-30^{o}C (60% Relative Humidity) and 45-50^{o}C (75% Relative Humidity).[51] At regular intervals, the films are checked for any physical change and drug content to see if the concentration of the active ingredient has dwindled over time or change in release profile. Stability studies on the optimized formulation of oral film is carried out to determine the effect temperature and humidity during storage, would have on the stability of the drug. The film can be stored in an

aluminium foil and subjected to stability at room temperature. The sample can be withdrawn at 90 days and 180 days and subjected to disintegration test as well as in vitro dissolution studies. Ali *et al* 2016 had reported an analysis of oral films of diazepam each week for a period of three months for drug content as well as use of hand to determine texture.[6]

3.4 In-vitro disintegration test

Disintegration time gives an indication of film break up features and predicts dissolution characteristics of the film. To carry out this test, the film is placed on a stainless-steel wire mesh and submerged in 10 mL of distilled water. The time required for the film to break was noted as *in-vitro* disintegration time.[7] Other studies use a different medium such as phosphate buffer, accompanied by intermittent stirring.[44]

3.5 In-vitro dissolution studies

Dissolution study is carried out to determine the release profile of the active drug from the oral film. It is done using the USP dissolution apparatus, operated at the rotation speed of 50 revolutions per minute and media of 900ml kept at a constant temperature of $37\pm0.5^{O}C$. A given sample is withdrawn at predetermined time interval, and rapidly replaced with same volume of fresh dissolution medium to maintain a sink condition. The quantities withdrawn are analyzed using spectrophotometer at a specific wavelength of the active drug and the obtained values are related to the amount of drug released with respect to time**.**

3.6 Permeation studies

Permeation studies measure the amount of drug that goes across a given area of a biological membrane such as that of the oral mucosa. To determine the flux of pharmaceutical active ingredient across the oral mucosa an artificial mucosal membrane or membranes of animals such as rabbit, can be used. The membrane is used in a modified Franz diffusion cell to create two chambers (donor and receptor chambers). The receptor chamber is filled with phosphate buffer of pH 7.4, but the oral film placed in the donor chamber while the membrane is kept stable. Aliquot samples taken from the receptor chamber are rapidly replaced with fresh phosphate buffer to maintain a sink condition. The aliquot samples are analysed for the concentration of the pharmaceutical active that has permeated membrane. The whole apparatus is maintained at a temperature of $37^{0}C$ using a water jacket.

4.0 Newer strategies for Oral films

In recent formulations of oral films, therapeutic proteins and nano-sized drug actives have been incorporated.

4.1 Delivery of therapeutic proteins and peptide products

The functionality and efficacy of therapeutic proteinous products is intrinsically linked to their specificity, and are sensitive to denaturation and degradation as they traverse the harsh conditions of the gastrointestinal tract. Delivery of this class of drugs as oral dosage forms has been an on-going challenge. Although some of these are already being developed in other dosage forms and at different stages, proteins and peptides all have good potentials for delivery as oral films to achieve better therapeutic efficacy while circumventing unfriendly conditions of the gastrointestinal tract. Beyond fast onset of action and mucoadhesion necessary in uncooperative patients, the advantage of high vascularization of the buccal cavity, low enzymatic degradation are strong points to move for oral film delivery of proteins and peptides. Insulin, desmopressin, octreotide and calcitonin are some possible biopotent proteins and peptides for therapeutic use as oral films.[8]

Challenges: One major challenge in delivery of proteins and peptides as oral is interractions between film excipients and the proteins or peptide drugs. This is particularly so since proteins' functionality is directly related to their structures. Hence any formulation will ensure that the protein structure eliciting therapeutic activity is maintained and preserved as such. Secondly, proteins are macromolecules and will present the challenge of absorption via the buccal which possess tight junctions. *Possible solutions:* Techniques of employing penetration enhancers which will disrupt these tight intercellular junctions increase fluid environment of the membranes or decrease the viscosity of its secreted mucus to allow for improved permeation. This approach together with timely drug liberation is being applied in oral film delivery to overcome the challenge.

4.2 Incorporation of nanoparticles in oral films

The challenge of poor solubility, dissolution and permeability associated with drugs in class II and IV of the Biopharmaceutical Classification system has necessitated some being entrapped in nanosized carriers or as nanosized particles and then impregnated in oral films. Improved bioavailability has resulted from such approaches. Three nanosized materials have been reportedly used, in literature, to incorporate drugs onto oral films. These are niosomes, nanospheres and nanosuspensions.[52], [53], [41] Niosomes are closed bilayer vesicles formed by

self-assembly of non-ionic surfactants and cholesterol in aqueous media. Structurally, niosomes are like liposomes but have better size flexibility, fluidity and stability, hence are easy to handle or store. Niosomes have good compatibility with drug and film forming polymers likely due to their non-ionic nature and non-immunogenic form[54], [53] prepared niosomal formulation of metroprolol tartrate incorporating it into oral films of hydroxypropyl methyl cellulose (HPMC) E15 and methyl cellulose. The oral film of niosomal metroprolol tartrate enhanced the drug bioavailability (91%) over the oral tablet (39%), even showed a prolonged therapeutic release over the oral film of the drugs not in nanosize**.** Nanospheres on the other hand being very tiny solid spherical drug stores could be formed from solid lipid nanoparticles. Al-Dhubiab (2016) experimented with Zolpidem nanospheres reportedly prepared by double emulsion solvent evaporation and loaded them unto buccoadhesive films made of blend of different film polymers of HPMC, Eudragit®, and carbopol.[41] The prepared films were evaluated and the drug release was seen to depend on film composition. In vivo studies as published revealed that oral film with incorporated zolpidem nanospheres improved drug absorption with a higher plasma concentration than conventional oral administration. Also, it took a longer time to reach the maximum plasma concentration signifying that nanosphere impregnated films can provide sustained drug release.[41]

Cefpodoxime proxetil, a BCS class IV broad spectrum antibiotic has limited oral bioavailability. To improve oral bioavailability, its nanosuspensions have been delivered through oral fast dissolving film.[52] Interestingly Patel and Shah (2015) had also attempted to improve bioavailability of domperidone, an antinauseating agent, by formulating nanosuspension of it using high speed homogenizer and incorporating it in oral film of HPMC E5 and Sodium Dodecyl Sulfate(SDS).[36] The films were compared with normal sized domperidone impregnated films. Films with the domperidone nanosuspension were reported to have high permeability (74%) and dissolution rate than those of the latter (22%) but with similar stability.

CONCLUSION

As the quest for better dosage forms to meet patient needs and promote acceptability is on-going, oral films technique will continue to be a delivery system not to be despised or discarded in a hurry. But update in the available knowledge and formulation skills continues to be a necessity to maximize the plethora of opportunities that this innovative system of delivery can offer.

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CONFLICT OF INTEREST

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Mfon and Daniel sourced for the materials, Daniel wrote the article, Each author approved the work for publication.

REFERENCES

1. Carter S J (2008) Cooper and Gunn's Dispensing for Pharmaceutical students 12TH edition cbs Publishers and Distributors Pvt. Ltd. New Delhi 8-11.
2. Aulton M E and Taylor KMG (2013) Aulton Pharmaceutics: The Design and manufacture of medicine 4th edition. Elsevier, London.
3. Pallavi P and Shrivastava S K (2014) Fast Dissolving Oral Films: An Innovative Drug Delivery System. *International Journal of Science and Research* (IJSR) Volume 3 Issue 7, July 2088-2093.
4. Srinivasan S (2016) Oral films: A look back Shanmugam, Clin Pharmacol Biopharm, 2016; 5: 2 http://dx.doi.org/10.4172/2167-065X.1000e124
5. Deadman LLF; New Impregnated or Coated Films. GB 1061557, 1964.
6. Ali MS, Vijendar C, Sudheer Kumar D and Krishnaveni J (2016). Formulation and Evaluation of Fast Dissolving oral films of Diazepam *Journal of Pharmacovigilance*, 4: 210.
7. Mishra R and Amin A (2011) Manufacturing Techniques of Orally Dissolving Films *Pharmaceutical Technology*, 35(1).
8. Castro PM, Fonte P, Sousa F, Maureira AR, Sarmento B and Pintado M E (2015) Oral films as a breakthrough tools for oral delivery of proteins/peptides. Journal of Controlled Release, 211: 63-73.
9. Yasuhiro Tsumea, Deanna M. Mudiea, Peter Langguthb, Greg E. Amidona, and Gordon L. Amidona(2014), The Biopharmaceutics Classification System: Subclasses for in-vivo predictive dissolution (IPD) methodology and IVIVC. *European Journal of Pharmaceutical science*, 57: 152–163.

10. Patel Priti, Patel Jaymin, Patel Kaushika, Nihar Shah and Shah Shreeraj (2015) A Review on Fast Dissolving Sublingual Film *Journal of Pharmaceutical and Bioscientific Research*, 5(3): 279-285.
11. Smart J D (2005) Buccal drug delivery. *Expert Opinion on Drug Delivery*, 2(3): 507-17.
12. Jain N, Bansal T, Nirmal J, Khar RJ, Kwan KC et al(2013) Biopharmaceutics and Pharmacokinetics in: Khar R K, Vyas SP, Ahmad F J, and Jain GK(2013) The Theory and Practice of Industrial Pharmacy(4th edition) CBS Publishers and Diatributors PVT Ltd New Delhi.
13. Hariharan M, Bogue (2009) A. Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms. *Drug Deliv Technol*, 9(2): 24-9.
14. Hoffmann E M, Breitenbach A & Breitkreutz J(2014) Advances in orodispersible films for drug delivery. *Expert Opin. Drug Deliv*., 2011; 8(3): 299-316.
15. Jadhav YG, Galgatte UC, Chaudhari PD (2013). Challenges in formulation development of fast dissolving oral films. *Indo Am J Pharm Res*., 3: 1746–1751.
16. www.alibaba.com (last accessed December 28, 13:10 pm).
17. www.mouthdissolvingfilms.com (last accessed December 28, 12.45pm).
18. Mishra R and Amin, A (2007) *Pharm. Technol. Eur*., 19(10): 35–39.
19. Shamma R & Elkasabgy N (2016) Design of freeze-dried Soluplus/polyvinyl alcohol-based film for the oral delivery of an insoluble drug for the pediatric use, *Drug Delivery*, 23: 2, 489-499, DOI.
20. Sandeep Karki, Hyeongmin Kim, Seon-Jeong Na, Dohyun Shin, Kanghee Jo, Jaehwi Lee(2016) Thin films as an emerging platform for drug delivery. *Asian Journal of Pharmaceutical Sciences*, 11: 559–574.
21. Genina N, Fors D, Vakili H, et al.(2012) Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques. *Eur J Pharm Sci*., 47: 615–623.
22. Davidson RS, Kehoe GS (2004). Water-soluble film for oral use EP1532973.
23. Morales JO, McConville JT (2011) Manufacture and characterization of mucoadhesive buccal films *Eur J Pharm Biopharm*, 77: 187–199.
24. Repka M et al. (2002) "Hot Melt Extrusion," in Encyclopedia of Pharmaceutical Technology, J. Swarbrick and J. Boylan, Eds. (Marcel Dekker Inc., New York, Vol. 2, 2nd Edition, pp. 1488–1504.

25. Arya A, Chandra A, Sharma V and Pathak K Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form *Int. J. Chem. Tech. Research*, 2010; 2(1): 578–583.
26. Sharma D, Kaur D, Verma S, Singh D, Singh M, Singh G, Rajeev G Fast Dissolving Oral Films Technology: A Recent Trend For An Innovative Oral Drug Delivery System *International Journal of Drug Delivery*, 2015; 7(2): 60-75.
27. Frey P (2006) Adhesive Research Film Strips and Pharmaceuticals Available from: http://www.adhesivesresearch.com/Files/ MPS%20Winter%2006%20Film% 20Strips%20&%20Pharm.pdf
28. Amin PM, Gangurde AB, Alai PV (2015). Oral film technology: challenges and future scope for pharmaceutical industry. *Int J Pharm Pharm Res.*, 2015; 3: 183–203.
29. Ayorinde J O, Effiong Daniel E and Michael Odeniyi (2018) Design and Evaluation of Oral Dissolving Films of Chlorpheramine From Native and Modified Enterolobium cyclocarpum Gum. African Journal Biomedical Research, 21(2): 175-182.
30. Jaiyeoba Odeniyi M, Ayorinde J O, Jaiyeoba KT (2013) Oral dissolving films of Chlorpheniramine maleate from Wheat Starch/Polymer Blends *Nigerian Journal of Pharmaceutical and Applied Science Research*, March 2013; 2(1): 25-32.
31. Ayorinde J O, Odeniyi M O and Balogun-Agbaje O (2016) Formulation and Evaluation of Oral Dissolving films of Alodipine Besylate using blends of starches with Hydroxypropylmethyl cellulose *Polim Med*, 46: 1-7.
32. Xiao-Qin Li, Zhao-Ming Ye, Jian-Bing Wang, Cai-Rong Fan, Ai-Wu Pan, Cong Li , Ren-Bing Zhang(2017) Mucoadhesive buccal films of tramadol for effective pain management, Rev Bras Anestesiol, 2017; 67(3): 231-237.
33. Pakorn Kraisit, Sontaya Limmatvapirat, Manee Luangtana-Anan, Pornsak Sriamornsak(2017) Buccal administration of mucoadhesive blend films saturated with propranolol loaded nanoparticles Asian journal of pharmaceutical Sciences, 2018; 13: 34–43.
34. Kaur A and Kaur G(2012) Mucoadhesive buccal patches based on interpolymer complexes of chitosan–pectin for delivery of carvedilol. Saudi Pharmaceutical Journal, 20: 21-27.
35. Prasanth Viswanadhan Vasantha, Ayarivan Puratchikody, Sam Thomarayil Mathew, Ashok Kumar Balaraman Development and characterization of Eudragit based mucoadhesive buccal patches of salbutamol sulfate. Saudi Pharmaceutical Journal, 2011; 19: 207–214.

36. Rakesh Patel and Dushyant Shah (2015) Nanoparticles loaded sublingual film as an Effective Treatment of Chemotherapy Induced Nausea and Vomiting. *Int. J. Pharm Tech Res.*, 2015; 8(10): 77-87.
37. Murata Y, Isobe T, Kofuji K, Nishida N, and Kamaguchi R(2013) Development of Film Dosage Forms Containing Miconazole for the Treatment of Oral Candidiasis Pharmacology & Pharmacy, 2013; 4: 325-330 Published Online June 2013 (http://www.scirp.org/journal/pp)
38. Chougule P C, Bhat M R, Chimkode R M (2017) Design and Evaluation of Formulated Mouth Dissolving Film of Domperidone and Study the Effect of Concentration of Polymers on Drug Release. *Asian Journal of Pharmaceutics*, Oct-Dec 2017; (Suppl) • 11 (4) | S846.
39. Khan S, S. Boateng J, Mitchell J, and Trivedi V(2015) Formulation, Characterisation and Stabilisation of Buccal Films for Paediatric Drug Delivery of Omeprazole. *AAPS Pharm Sci Tech*., 16(4): 800–810.
40. Augusthy A R, Vipin K V, Sarath Chandran C, Muhammed Nizar AV, and Sreeraj K(2014) Formulation and Evaluation of Rabeprazole Buccal Patches. Research and Reviews: Journal of Pharmaceutics and Nanotechnology Available from: https://www.researchgate.net/publication/308890779 [accessed Dec 28 2018].
41. Al-Dhubiab B E (2016) In vitro and in vivo evaluation of nano-based films for buccal delivery of Zolpidem. *Braz Oral Res.*, Nov 28; 30(1): e126. doi: 10.1590/1807-3107BOR-2016.vol30.0126
42. Hanif M, Zaman M and Chaurasiya V (2015) Polymers used in buccal film: a review Designed. *Monomers and Polymers*, 18(2): 105-111.
43. Bonsu M A, Ofori-Kwakye K, Kipo S L, Boakye-Gyasi M E, Fosu M A (2016) Development of Oral Dissolvable Films of Diclofenac Sodium for Osteoarthritis using Albizia and Khaya gums as Hydrophylic film formers. *Journal of Drug Delivery* www.hindawi.com/journals/jdd/2016/6459280
44. Anoop Kumar Pankaj Kumar Sharma, Asghar Ali (2013). HPMC/CMCC based fast dissolvable oral films of an anxiolytic: in vitro drug release and texture analysis *International Journal of Drug Delivery*, 5: 344-352.
45. Kumar S, Gavaskar B, Sharan G, Rao YM, (2010) Overview on Fast Dissolving Films, *International Journal of Pharmacy and Pharmaceutical Science*, 2: 29-33.

46. Siddiqui, N., Garg, G., & Sharma, P. kumar (2011) A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and their Patents. Advances in Biological Research, 5(6).
47. Patil P and Shrivastava S K, (2014) Fast Dissolving Oral Films: An Innovative Drug Delivery System *International Journal of Science and Research (IJSR*), 3(7): 2088-2093 www.ijsr.net
48. M Irfan, S Rabel, Q Bukhtar, M I Qadir, F Jabeen, A Khan(2016)Orally disintegrating films: A modern expansion in drug delivery system *Saudi Pharmaceutical Journal,* 2016; 24: 537–546.
49. Mahboob MBH, Riaz T, Jamshaid M, Bashir I and Zulfiqar S (2016) Oral Films: A Comprehensive Review. *International Current Pharmaceutical Journal*, 5(12): 111-117.
50. Li L Naini V, and Ahmed S U (2007), Utilization of a modified special-cubic design and an electronic tongue for bitterness masking formulation optimization. *Journal of Pharmaceutical sciences,* 96: 2723-34.
51. Khanusiya A Qadir, Charyulu RN, Prabhu P, Bhatt S and Shastry CS(2012), 3 Formulation and evaluation of fast dissolving film of loratadine for sublingual use *International Research Journal of Pharmacy*, 3(7): 157-16.
52. Singh C K, Tiwari V, Shankar R, Mishra C P, Sarvesh Jain, Sandeep Jain and Sandhya Jaiswal (2016) A short review on oral fast dissolving film containing Cefpodoxime proxetil nanoparticle. *World Journal of Pharmacy and Pharmaceutical sciences*, 5(1): 1549-1577.
53. Ayat Allam and Gihan Fetih (2016)Sublingual fast dissolving niosomal films for enhanced bioavailability and prolonged effect of metoprolol tartrate. *Drug Design Development and Therapy*, 2(10): 2421–2433.
54. Seleci D A, Muharrem Seleci M, Walter J G, Stahl F, and Schepe T(2016) Niosomes as Nanoparticular Drug Carriers: Fundamentals and Recent Applications *Journal of Nanomaterials* Volume 2016, Article ID 7372306, 13 pages.