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(REVIEW ARTICLE)

The oral film delivery- Application of nanotechnology and potential in medication adherence

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Abstract

The use of medicines is an irreplaceable necessity in healthcare delivery. Application of advancing technology, especially the oral film techniques in pharmaceutical production has resulted in medicine availability in a trendy, readily acceptable and usable form, oral films. Although many literature abound on oral film delivery systems, there is paucity of work on recent incorporation of nanotechnology concepts and the potentials of this delivery system in improving medication adherence. Thus this work focuses on bridging this obvious gap. It reviews published works on the oral film technology, profiling recent advances in the nanoparticles incorporated into films, and necessary considerations in such formulations. It also explores oral films as a delivery system for improved adherence. Online search for articles on oral films production, marketed nanoparticle-based oral films, and the extensiveness of medication non-adherence was carried out using websites of researchgate, google search, film manufacturer's websites, google scholar and pubmed. Search terms used were 'marketed oral films', 'available medicines as oral films', 'nanotechnology in oral film production', 'oral film techniques', 'oral films manufacture + disease condition' and 'medicine adherence'. Articles were sorted on the basis of currency and practicality of information. The market space of oral film is growing steadily. Present use of oral film technology in delivering antipsychotics, antihistamines and analgesics is well received. Many drugs are currently incorporated into films in nano-sized forms to improve dissolution, bioavailability and effectiveness as revealed by the search. More can be achieved if this technology is extended to cover other classes of drugs such as antihypertensives, antiulcers and agents indicated for other chronic conditions. Fully exploring the unique features of the conventional oral films dosage forms and those embedded with nanoparticulate drug forms, therein lies the potentials to contribute to significant improvement in medication adherence even in chronic conditions.

Keywords: Oral films; Nanobased oral films; Nanotechnology; Medication adherence; Chronic conditions

1. Introduction

For its convenience, compliance and cost effectiveness, the oral route continues to be the delivery route of choice, constituting an essential part of the pharmaceutical industry [1]. Especially so is the oral solid dosage forms because of added advantage of available technology, stability and ease of transportation. But of the several solid oral dosage forms, oral films stand tall as an advanced delivery system [1].

Oral thin films, fast dissolving oral films, oral film strips, or oral dissolving films are all different terms describing the same drug delivery system. Oral films are stamp-sized, flat-shaped therapeutic delivery systems usually with fast onset

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of action but administered orally. They are usually made up of hydrophilic polymers with incorporated active drug. As at 2017, the global oral thin films market was valued at US$ 2,100 Million and is expected to grow at a Compound Annual Growth Rate (CAGR) of 13.0% between the years, 2018 and 2026 [2, www.transparencymarketresearch.com/oral-thin-films-market]. Oral films are advanced oral solid dosage forms prepared, in many cases, to disintegrate rapidly in the mouth, bypassing hepatic and gastric degradation but to deliver drugs into systemic circulation. Thin films can enable rapid release of ingredients (usually 10-30s), quick onset of action or sustained release, providing convenience for pediatric and geriatric patients where dysphagia is readily encountered [3, 4].

So much has been published in journal articles (both online and in print) about oral film delivery systems and so much progress is being made in the formulation of many new medicines as films, as well as in the application of advanced technology in this delivery system [1-5]. However, there is paucity of published work on the application of nanotechnology in oral film dosage form and its application in improving medication adherence. This write-up thus aims at bridging this observed gap. It gives an overview of the oral film technology, its formulation considerations, and the progress in the application of nanoparticulate forms of drug in preparation of films. It also attempts to present factors to consider during such incorporation and the potentials of using this delivery system in improving medication adherence. Such information can be a quick reference and foundation for researchers and manufacturers of oral films as they attempt the design and development of this solid oral dosage form. A good background of this delivery system is a way to start.

1.1. Brief History

The demand for oral films, an advanced therapeutic dosage form, has steadily increased since its introduction in the literature in the 1960s. From then on, oral films have been available in the market as over the counter products such as breadth freshening strips, vitamin strips, anti-allergics, and other over-the-counter products. The pharmaceutical companies in recent times are now exploring the advantage of prescription drugs as oral films, since a prescription for it will not be substituted with another dosage form [3]. Currently in the market, several prescription only medicines (POM) have been produced as oral films and the number keeps increasing. The first prescription drug in 2010 (approved by Food and Drug Administration, USA) presented as oral films was Zuphlenz®, Ondansetron oral film indicated for emesis and nausea resulting from chemotherapy and radiotherapy. Applied Pharma Research on the other hand in 2012, marketed successfully Zolmitriptan oral films indicated in migraine treatment [3, 5, and 6]. From that time of first mention in literature onwards, oral films of newer classes of drugs have been introduced into the market and acceptance from patients and practitioners seen [7]. Some notable milestones in the development of oral films is presented in table 1.

Table 1 A tabular presentation of notable milestones in oral film delivery systems

Milestones in oral films Developments	Oral films in patent literature	Oral films as consumable products e.g Listerine	Other over the counter drugs as oral films e.g Gas-X(simethicone), Chloraseptic (7-Benzocaine)	First FDA approved prescription only medicine as oral film (Zuphlenx®-Ondansetron)	Insulin oral film patent granted to Pharmedica Ltd	Exservan® (Riluzole) by Aquestive therapeutics presented as oral film
Time lines:	**1960**	**2001**	**2001-2005**	**2010**	**2018**	**2019**

Source: [3, 5]

2. Oral films: advantages and disadvantages

Oral films have advantage in dosing convenience, ease of administration with no need for any adjunct solvent, and especially for patients with swallowing problems: pediatrics, geriatrics, and those with dysphagia, having fear of choking, as well as emetic patients [4, 7]. Oral films have good stability and need no dosage form reconstitution [1]. These good features can result in improved patient acceptance and, understandably, adherence. Oral films can be for systemic effect as well as have local action (within the buccal cavity). This solid dosage form is a versatile delivery system whereby several drug actives at different doses can be incorporated. This delivery system is, however, not without demerits such as a limited dose capacity of drugs incorporated, challenge of taste masking for very bitter-tasting drugs, and challenge of achieving dose uniformity. The search and selection of suitable polymers to form oral films can be a tall order and extensive research is on-going to enable different drugs to be incorporated into these films and to overcome certain manufacturing bottle-necks [3, 4].

2.1. Drug absorption from oral films

Drug administered via all routes, except the parenteral ones, requires absorption; that is uptake of the drug from the point of administration, through the epithelium /endothelium into systemic circulation to the site of action. Thus, drug released from oral films is transferred from site of administration into systemic circulation. The oral mucosa responsible for absorption of drug from the oral films include the sublingual (under the tongue), buccal (inside the cheeks), gingival (the gums) or the palates. These oral environments are richly supplied with blood vessels, the sublingual region ranking topmost of the four. Hence the sublingual route, with high permeability achieves high bioavailability and rapid onset of action [8]. As saliva mixes with the dosage form (oral film) on administration, the film polymer (usually hydrophilic) gradually disintegrates or dissolves, releasing the drug content. The drug released penetrates the oral mucosa and is absorbed into the reticulated and jugular veins, then drained into the systemic circulation. This path circumvents hepatic (first pass) and gastrointestinal metabolism [9]. This route of administration, therefore, improves bioavailability, reducing associated untoward effects. Drug absorption through the cells in the oral mucosa can either be transcellular (across) or between cells (paracellular). Those with poor aqueous solubility use transcellular absorption taking advantage of the lipid bilayer of the cell membranes, whereas the readily soluble drugs are absorbed via the paracellular even though, usually, both routes are possible [10].

2.2. Oral films: Formulation considerations

To formulate a mechanically robust yet therapeutically effective and acceptable oral films, some necessary factors must be put into consideration**;**

2.2.1. Active ingredients to be used

In the formulation of oral films, not all active ingredients qualify. Since films are stamped sized with the polymer used occupying the larger percentage of composition, drugs with high molecular weight, and very large dose of administration are hardly used [11]. Beyond the concern of dose to be loaded, solubility, taste, thermal sensitivity, and stability of drug actives to be incorporated in the oral films are considered. For instance very bitter drugs will present a challenge of taste masking while not compromising stability; drug solubility during manufacture contributes to dose uniformity and sensitivity to heat determines method of drying [10]. Drug interaction of active ingredients with other excipients, dose uniformity to ensure safety are other factors for consideration. Dose uniformity is particularly useful so as to avoid under -doses or overdoses especially for prescription drugs. Among the low dose drugs that qualifies and has been formulated as oral films are monteleukast (leukotriene receptor antagonist), diazepam (antianxiety), amlodipine (antihypertensives), and diclofenac (analgesic) [3].

2.2.2. Film polymer selection and safety

Apart from the active drug, excipient composition in oral film is very important. A principal excipient is the film forming polymers. A necessary caution (based on sound scientific principles) is exercised in its selection and safety. Consulting several published literature on these polymers and their unique features will be a good step before selection [12].The film forming polymer must be nontoxic, non-irritant and must be impurities-free [7]. Among the polymers readily used are starch, maltodextrin, pullulan, gums, gelatin and cellulose, and their modified forms. Generally, most of these polymers employed are generally regarded as safe since in most cases they are already approved by regulatory authorities for use in the food and drug industries. These polymers used can be natural (e.g pullulan, pectin, starch and cellulose) semisynthetic (hydroxypropyl methylcellulose HPMC, caboxy methylcellulose, CMC) or synthetic (e.g carbopol, sodium carboxy methylcellulose and polyvinyl alcohol) depending on the need and availability. A good knowledge and understanding of the features of these polymers is necessary for selection, and in developing a good oral film product. At times a good final formulation is a combination of two or more of these polymers to improve their film forming characteristics [1, 11, and 13].

2.2.3. Choice of other excipients

Other excipients such as absorption enhancers, disintegrants, plasticizers, colorants and sweeteners are chosen and incorporated depending on the desired final product. For immediate release oral films, a good disintegrant/super-disintegrant and wetting agent would be very important [3]. For sustained released oral films, disintegrants are excluded but suitable mucoadhesives (for site specific application) and absorption enhancers play key roles so that as the products are attached to mucosal membrane, their content released by gradual erosion are readily absorbed. So depending on the desired final product, the appropriate excipient in the right amount is incorporated for use [7, 14].

2.3. Manufacturing techniques of Oral films

Figure 1 shows the several techniques for manufacture of oral films. The casting method appears to be the most popularly used method in laboratory works as the technology is readily achievable [1, 15]. In this method, prepared solutions, dispersible mixtures or semi-solid dispersions of the drug, film forming polymer, and other necessary excipients are poured into containers which serves as moulds and casted. These dry out as films. The drying could be done using an oven or a freeze dryer depending on the thermo-labile nature of the drug. Any entrapped air during mixing is removed by vacuum before drying to ensure dose uniformity [15].

During extrusion, a mixture of dry solid masses of drugs, film polymer and excipients or their solid dispersions are forced through an extruder (usually having high temperature zones). The melted mass formed during extrusion are then dried or casted in containers that are used as moulds [3].

The printing method of film manufacture is an advancement in the principles used in printing of medicine labels and imprints on solid dosage forms. It is a three dimensional (3-D) printing used. Therapeutic agents prone to denature by heat are printed onto already prepared dried placebo films [16]. The Flexographic or injet printing technology is most popular employed in this regard. While the earlier incorporates the drug active using rotating rollers, the later does so as drops of concentrated solution of the drug on preformed films. This latter would not be appropriate for agents that are subject to hydrolysis or solvolysis. Proteins and peptide drugs, using this method, have been reportedly produced as oral films [3, 16]

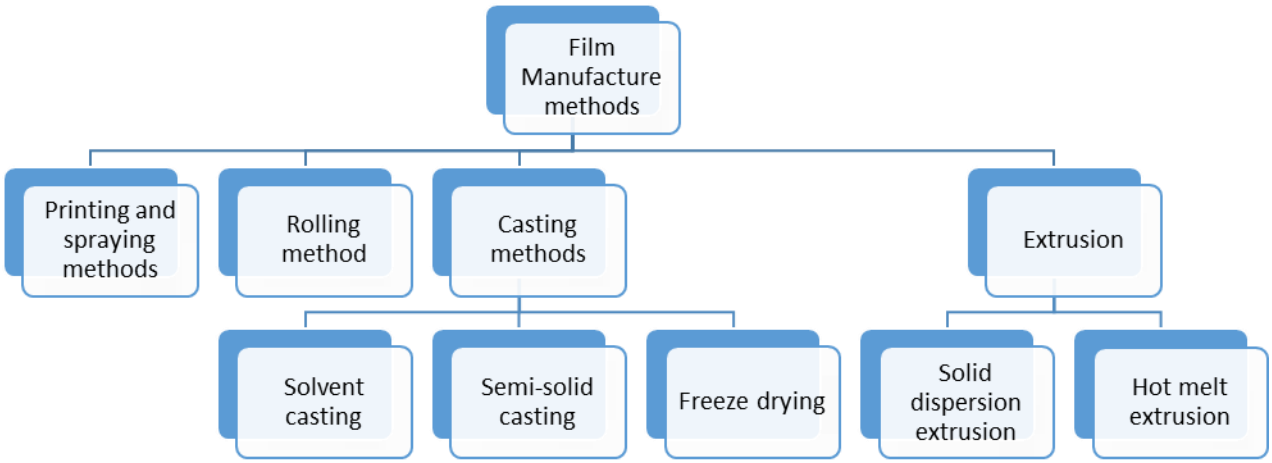

Figure 1 Manufacturing methods of Oral films

2.4. Classification of oral films

Films used as oral dosage forms can be classified as oral dissolving films or dispersible ones depending on the solubility of the active drug in the film forming polymer solution (see Figure 2). It can be described as flash release (immediate release) or prolonged release, based on the release mechanism and onset of action. Both types can further be classified as buccal (if released in the mouth), sublingual (under the tongue) palatal (placed on the palate) or gingival (if place on the gum). A sound classification using the peculiar properties of films has been published [3, 18]. Beyond this, pharmaceutical companies have shown innovation as they, employing advancing technology, develop their unique patented film bases for drug incorporation as presented in table 2 with their peculiar features. Figure 3 shows some commercially available films in their marketed packaged forms.

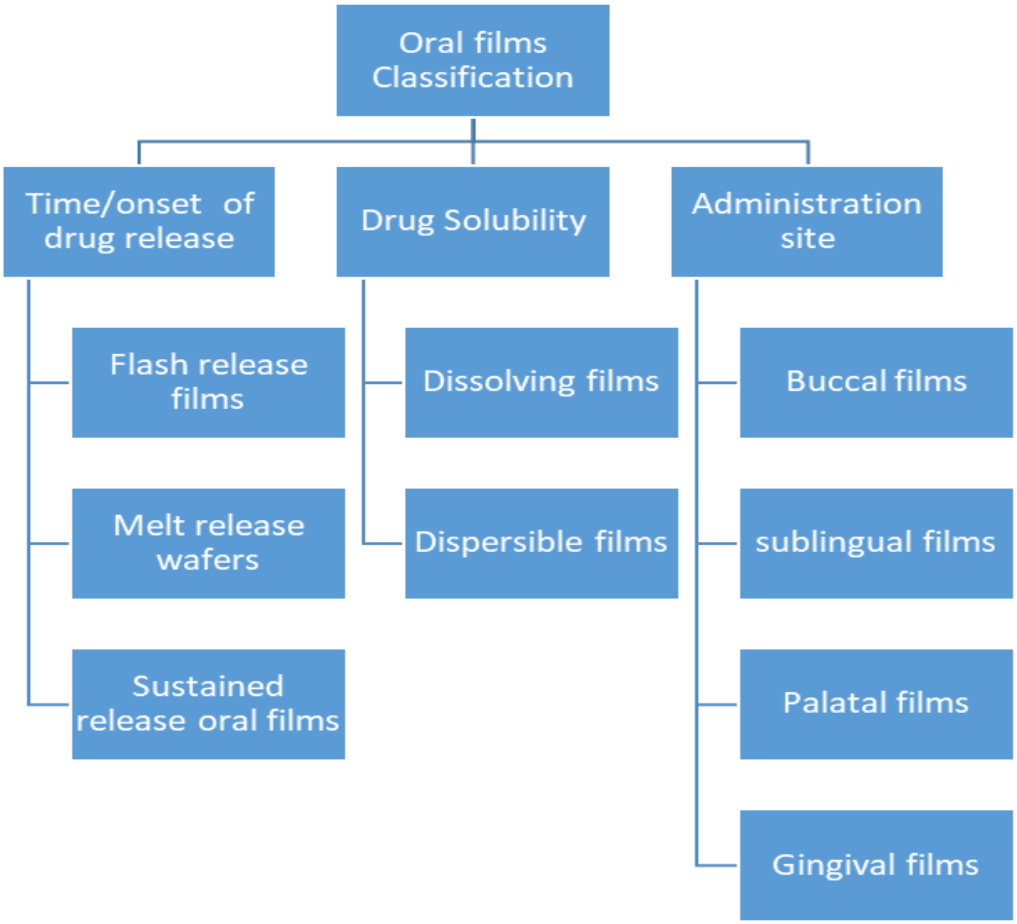

Figure 2 Oral film classification

Table 2 Some commercially available patented film technologies

Patented films	Unique features	Year of Patent	Company
XGel™	The film is made from genetically modified organism (GMO). Being of non-animal origin, it is suitable for vegetarians. It can be layered, colored, and masked with different drugs readily incorporated. Solubility is in both hot /cold water		Meldex international (Developed by Bioprogress Technology, United Kingdom)
Wafertab film™	Accurately dosed active ingredient is integrated into an ingestible strip (e.g., premanufactured XGel ™). Several of such strips with incorporated drugs can be bonded to give shape of a wafer. Wafers can be well flavoured and rapidly dissolves to release drugs once the strip is in contact with saliva in the mouth. Useful for presenting medicines requiring fast onset of action.		LTS Lohmans
Soluleaves™	Soluleaves™ films can be designed to adhere to mucous membranes, releasing the active ingredient slowly over 15 min or to dissolve		Bioprogress Technologies

	rapidly on contact with saliva, quickly releasing the active ingredients. It can be used for therapeutic agents as well as for nutritional purpose.		
Foam burst	This patented film is another variety of soluleaves™. It is usually formed when inert gas is passed into the film during production. This resulting film comes with honeycomb structure, and can dissolve rapidly with an appealing mouth sensation. It is readily applied by food and confectionary manufacturers as a means of carrying and releasing flavors	2004	Intelgenx Corp
Versafilm®	a versatile oral drug delivery technology that enables the development of oral thin films with improved product performance of rapid disintegration without the need for water fast buccal or sublingual absorption	2017	Intelgenx corp
Vetafilm™	Film technology platform of Intelgenx corp for veterinary use. They are oral films designed to adhere on contact to mucosa of animals, removing the need for syringe handling It is claimed by manufacturers to increase animal acceptance/ compliance and is customized for specific needs	2017	Intelgenx corp
Curefilm®	innovative oral thin film CUREfilm® is an oral soluble film technology platform by cure pharmaceuticals for oral drug delivery. It is claimed to allow optimal drug release profiles for better patient outcomes and experiences. It can load high dose of drug actives, easy to store and transport, achieves precision dosing for patient individualization. Formulations with this platform can be used in multiple final dosage forms based on the desired drug release profile and user experience.	2019	Cure Pharmaceuticals
Pharmfilm®	A unique and versatile technology for high-performance drug delivery. It is based on a polymeric matrix of hydoxypropyl methyl cellulose which can quickly dissolve with fast absorption achieved. It is claimed to be more stable and robust in comparison with other conventional films with similar loading capacity.	2012	Monosol Rx

Source: [1, 19, https://www.curepharmaceutical.com, https://www.aquestive.com]

Figure 3 Some commercially available oral films in their marketed packages

Source: [https://www.intelgenx.com]

3. Nanotechnology in oral films

Since the oral thin film medication are developed for swift, trendy and convenient oral administration of drugs, more medicines are being developed in this form to improve patient compliance. Various types of vaccines and hormones are being developed currently by pharmaceutical market players such as Aridis Pharmaceuticals and Aquestive Therapeutics [https://www.intelgenx.com, https://www.grantome.com]. Technological advancement in drug discovery and development processes, poor bioavailability of solid drugs, and inaccurate dosage in liquid formulations have expectedly continued to boost the market growth for oral films market whereas, challenges related to drug development and massive research investment required for creation of simple and novel formulation is expected to hinder the market [2, http//:www.transparencymarketresearch.com/oral-thin-films-market.html].

Exploring nano-sized materials (products of nanotechnology), has become a means to overcome the challenges of poor solubility and bioavalability in the pharmaceutical industry [20, 21]. Nanotechnology describes the science and engineering of production and use of materials, at the size of 10^{-9}m in dimension. As the sizes of particles gradually reduce and the visibility wanes off, the properties of the materials also change drastically.

Among the most common of nanosized particulate forms impregnated into oral films are;

3.1. Nanosuspensions

This colloidal dispersions of nanosized solids (whether amorphous or crystalline) has been a technique for improving dissolution of poorly soluble drug actives. Although agglomeration with resultant instability, is a common disadvantage of these nanoform preparations, use of polymeric surfactants as stabilizers have been applied to overcome it. Drugs in these forms have been incorporated in the formulations of liquid or solid dosage forms and preparations such as tablets, capsules and films [22].

3.2. Niosomes

These nanosized vesicles of non-ionic surfactants and cholesterol in aqueous medium have the active drug embedded within the core. The surfactants self-arrange as a bilayer that encloses the drug in an aqueous solution within it. Drugs that are either hydrophilic or lipophilic can be entrapped within the core of niosomes and can be released at a targeted site or at a controlled rate [23]. Niosomes have good stability and flexibility. Ayat and Gihan [24] prepared niosomes of metroprolol tartrate and embeded this within oral films of hydroxypropyl methyl cellulose (HPMC) E15 and methyl cellulose. The oral film impregnated niosomes of metroprolol tartrate enhanced the drug bioavailability and prolonged release of the drug when compared with the oral tablet [24].

3.3. Nanospheres

These tiny solid spherical drug stores generally have an active drug core covered by a polymer (usually poly lactic acid) layer. They could be formed from solid lipid nanoparticles. Many are made from polymers that are biodegradable, biocompatible and the size uniformity of nanosphere are influenced by the polymer type used. Nanospheres have been reported as good delivery systems since they completely entrap the drug and release same at the desired site [25].

3.4. Nanocomposites

These are nanosized combination products of organic materials (polymers) and inorganic solids. Usually the polymers are polysaccharides and the polylactic –co-glycolic-acid (PLGA) but clay and metallic oxides make the inorganic solids. These inorganic components are so employed to enhance the desired properties of the polymeric materials like permeability and conductivity [26]. Nanocomposites have found applications in orthopaedic use and in chemistry, and their use in drug delivery has been well reported in literature, although they may have limitations of insufficient homogeneity, and poor adhesion [27, 28].

Table 3 presents a list of published research works incorporating nanosized drug forms into oral films. It is instructive, however, to mention that to incorporate any of these nanosized forms into oral films drug delivery, two points must be considered. One is the physicochemical properties of the nanoparticles or nanoforms while the second is nanosized drug-excipient interaction. Physicochemical features of nanoparticles (which include particle size, crystalline structure, charge, and surface properties) can affect drug solubility during manufacture, the stability of final product, and the optimal interaction of film at the site of application. While smaller size of the particles can increase surface area with resultant improved absorption, the presence of surface charges can influence such absorption negatively and product stability.

Nanoparticles-based oral films can and has been designed and formulated to have different properties such as mucoadhesion, mucus-penetration, controlled release, and ease of deformation [29, 30, and 31]. For example, nanoparticles with low molecular weight polyethylene glycol (PEG) coatings have been reported to have reduced interaction with mucus, improving particle transportation through the mucus and mucosa, and enhance delivery into lymph nodes [31, 32]. The ideal size of nanoparticle for use in oral dosage forms, for optimal interaction at oral mucosa (whether 100-300nm) is yet to be evaluated comprehensively. But Hua *et al*., [31] had reported that electrostatic interaction between cationic nanoparticles and oppositely charged mucins impeded the particles through the mucus layer. Anionic nanoparticles on the other hand were able to inter-diffuse through the mucus network likely because of less electrostatic interaction with the mucus [33].

Second factor for consideration is nanoparticle excipient interaction. For effective delivery of the active drug from nanoparticulate impregnated oral films, the interaction of the nanoparticles with the film forming polymer and other excipients is essentials. Nanosuspensions, nanocrystals, nanoemulsions can on their own be unstable (due to agglomeration), incorporating them into film base may trigger instability, if appropriate investigation is not carried out, hence the need for adding stabilizers [21, 34]. Thus the nanoparticles should be stable, not interact when incorporated into the pharmaceutical film forming polymer, especially during manufacturing and storage. In addition, the formulation base (film forming polymer) should make possible that the product have a longer contact time with the oral mucosa for interaction at this site to optimize drug permeability and systemic absorption [33].

Table 3 List of some works on oral films with incorporated nano-sized drug particles

Class of drug	Example in oral film	Nanotechnology employed and method used	Advantage	Film forming Polymers used	References
Antibiotics	Cefpodoxime proxetil	Nanosuspension	Improved oral bioavailability		[35]
Antiviral	Herperitone	Nanosuspension by high pressure homogenization	Enhanced dissolution rate and oral bioavailability of the poorly water-soluble drugs.	HPMC	[36]

Antiinfective (Stomatitis)	Chlorhexidine	Nanocomposites	Prolonged effect of almost half a day Targeted delivery	Carmellose (Sodium carboxymethyl cellulose)	[29]
Anti-nauseating agent	Domperidone	Nanosuspension (high speed homogenizer)	Higher permeability and dissolution than normal coarse paarticles	HPMC with Carbopol as mucoadhesive and Sodium dodecyl sulfate as a wetting agent	[37]
Sedative-hypnotic	Zolpidem for insomnia	Nanospheres (double emulsion solvent evaporation)impregnated buccal film	Improved drug absorption and prolonged drug release	HPMC + Eudragit R L + Carbopol	[30]
Anti-anxiety	Buspirone hydrochloride	Nanoparticle (Nanoprecipitation)	Better physicochemical properties and optimum stability Sustained drug release	(PVA, HPMC E15, Maltodextrin, Sodium Alginate, HPMC E15 + PVA in 1:1 ratio)	[34]
Antihypertensive	Metoprolol tartrate	Niosomes	Improved drug bioavailability and prolonged release	Hydroxy propyl methyl cellulose (HPMC E15) and Methyl cellulose	[24]
Antihypertensive	Carvedilol	Nanosuspension into solidified hydrogel	Fast invitro release and enhanced invivo bioavailability	HPMC and Carbopol	[38]
Antihypertensive and antianginal	Lercanidipine Hydrochloride	Nanosuspension (evaporative antisolvent precipitation method)	Superior dissolution, increased permeability	HPMC, HPMC+PVA	[39]
Antihypertensive	Olmesartan medoxomil	Nanosuspension (antisolvent precipitation ultrasonication method)	Improved bioavailability, increased Cmax and AUC	Pectin and Hydroxyethyl cellulose	[40]
Antihypertensive	Captopril	Cellulose nanofibers as compatibilzers for delivery	Increased Cmax, AUC but decreased Tmax Increased oro-transmucosal absorption	Pullulan + HPMC	[41]

Antifungal	Griseofulvin	Nanoparticles by wet stirred media milling	Increased rate of dissolution	Pullulan	[42]
Antiepileptic	Midazolam Hydrochloride	Nanosuspension (Ultrasonic method)	Increased AUC, Cmax and decreased Tmax	HPMC + Pullulan matrix	[43]
Antidiabetics	Glimepiride	Nanosuspension loaded oral films by solvent casting	Improved bioavailability and stability	HPMC	[44]
Cholesterol lowering agent	Fenofibrate	Nanocrystal (wet media milling)	Enhanced dissolution, and improved *in-vivo* bioavailability	HPMC	[45]

4. Oral films in medication adherence

Oral films for its advantages, especially with incorporated nanoparticles, opens up potential for improved medication adherence. Medication non-adherence by patients, has been an impeding bog in the wheel of a smooth running healthcare system. Truth be told, good medicines, no matter the cost or technology employed, are of no good when not used. Non-adherence to prescribed medication delays quick recovery of patients, weighs on the minds of healthcare providers, adds to the rise in healthcare expenditure of the government and casts doubts on the reputation of pharmaceutical companies, raising concerns on the efficacy of their products [46]. The outcome of poor medicine adherence has implication on everyone, directly or by extension. It can hinder the therapeutic process in disease management, giving birth to medical complications, poor quality of life and even death [US Food and Drugs Administration portal, Medication Adherence https://www.fda.gov, Last accessed 24/07/2019].

The World Health Organization (WHO) defines medication adherence, also described as correctly taking medications, as the degree to which the pattern of medication use by the patient (with his awareness and consent) corresponds with the prescribed regimen. It is the extent to which patients take medication as prescribed by their licensed health care provider [World Health organization portal, Adherence to long term therapies; evidence for action, https:// www.who.org, Last accessed 18 /04/2020]. It could manifest at the point of initiation of therapy, implementation of it or during the persistence. Medication compliance or adherence, in this work, carry the same idea.

Medication adherence has been described by percentage rates on a scale of 0-100, indicating poor to excellent respectively [46]. Worldwide, with about 50% of adults having chronic medical conditions, 8% of pediatrics and the aging population facing the same medical challenge, the use and reliance on medicines is stretched. Poor adherence to medicines is understandably very common in patients with chronic conditions, although other reasons are possible (figure 4). In fact, 50% of patients on long term therapy are reported to be non-adherent [48]. Such huge figures when considered alongside those of patients with acute medical conditions, indicates a growing healthcare problem requiring strong conscious measures to reverse [48, World Health organization portal, Adherence to long term therapies; evidence for action, https:// www.who.org, Last accessed 18 /04/2020]. Yearly, the financial implications of medication non-adherence in Europe, the Americas, and Australia is in billions of dollars. In Asia and Africa, the statistics are no different. For example, a 2011 survey on outpatients visiting a Psychiatric hospital located in the South-south region of Nigeria revealed that 42.3 % were non-adherent. In Congo Democratic Republic, patients taking anti-hypertensives, had non-adherence rate as high as 54.2% [49, 50]. Poor adherence, such as these, results in increased cost of hospital admissions and management of complications. A Cochrane Review in 2002 as reported in the Pharmaceutical Journal revealed that devising effective ways to make patients follow medical recommendation, has far reaching effects on health outcome, than any treatment in itself [51]. One such effective means that can be employed is the use of an appealing, delivery system of oral films which can be a good angle to consider.

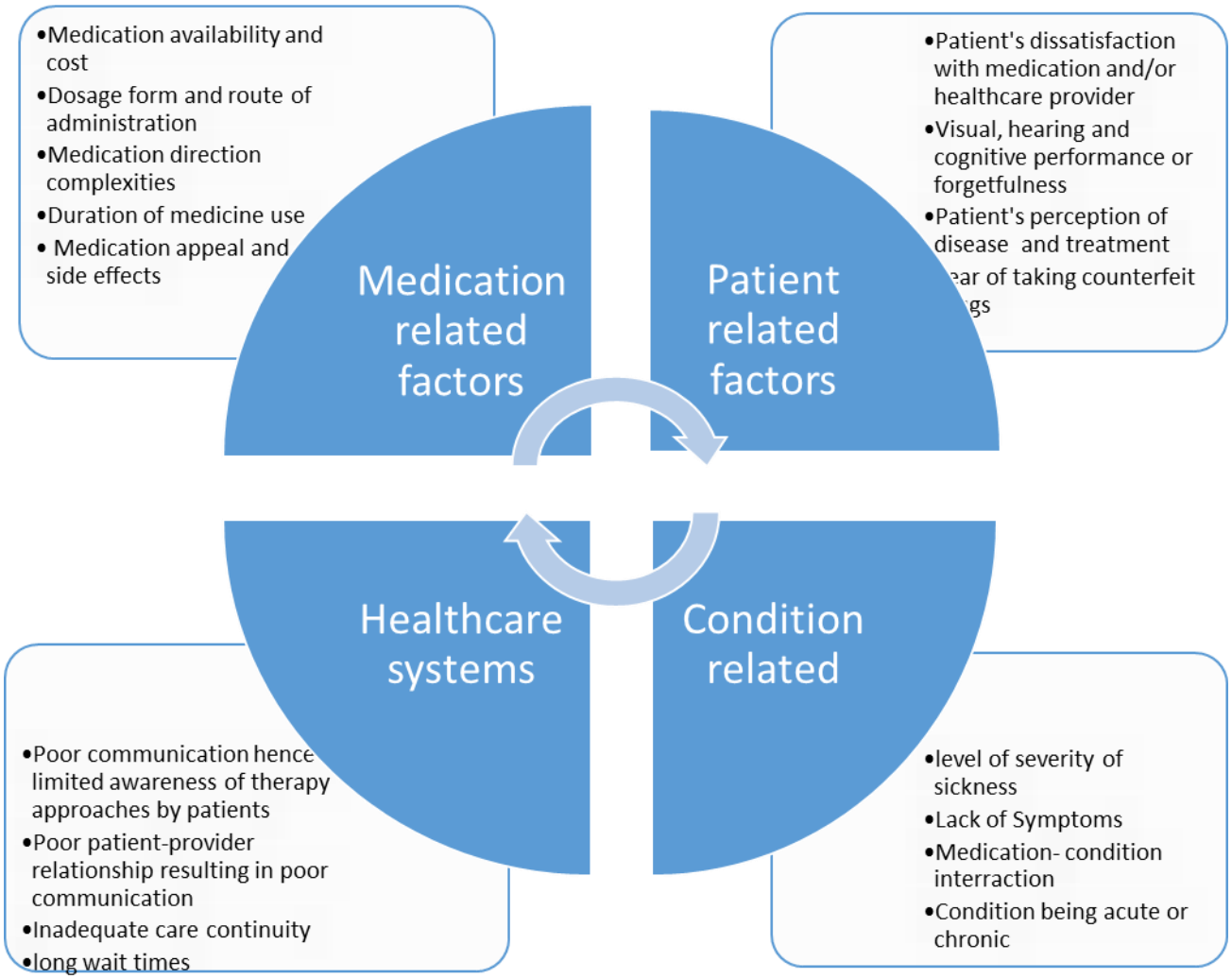

Figure 4 Possible reasons for Poor Medication adherence

Source: [47, 51, 52]

5. Some classes of drugs for consideration for Oral films to improve Medicine adherence

To redesign and change how drugs are developed and delivered can have a lasting impact for patients and caregivers. Such change brought through the application of oral film delivery (even incorporating nanotechnology) can contribute immensely to medicine adherence by removing the complexities in medicine use, but replacing these with appeal, trendiness and therapeutic efficacy. The Oral film, as an advanced solid delivery system, overcomes the challenges of modified oral solids and has been applied in a wide range of disease conditions, acute or chronic [5, 13, and 15]. Geriatrics, pediatrics and patients with diabetes, the bedridden and patients needing antiemetic can, and do benefit from oral film strips [7]. Table 5 shows drugs that have been formulated as oral films revealing their potentials to improve adherence to them.

5.1. Oral films in vaccine delivery

New vaccines are DNA based, liposomes, virus-like particles (VLP) based and are more effective. Published works abound on delivery of vaccines in the readily acceptable form of oral thin films [54, 55]. Oral film vaccine is an alternative, yet effective route of vaccine administration when compared with those of intramuscular (IM), subcutaneous (SC), and the per-oral (PO) routes [54]. This is especially so with the new types of vaccines. Additionally, only a small quantity of the vaccine is needed when presented as oral films because of overcoming first-pass hepatic degradation, and rapid mucosal and systemic immunity induction is achieved [55]. In these unique features, lie the potential for oral film vaccine to improve adherence.

5.2. Oral films of antihypertensives

Of the several cardiovascular conditions, hypertension rates highest in terms of number of sufferers and about 70% of these are resident in low- and middle-income countries. The prevalence of hypertension has been estimated to increase by 30% by the year 2025 [53]. Managing hypertension in patients involves treating high blood pressure by consistent use of prescribed medicines, managing mental stress other and medical conditions and periodic medical visits for check-ups and review [Hypertension. https://www.who.int/news-room/fact-sheets/detail/hypertension, Last accessed at 13/09/ 2019]. Non-adherence to such prolonged medication regimens is common. Report reveal that hypertensive patients form, approximately, 43% - 65.5% of patients who fail to adhere to prescribed regimens Adherence [56, Adherence to long term therapies, https://www.who.int]. Non-adherence to anti-hypertensives results in uncontrolled blood pressure and consequent complications. A higher percentage of hypertensive patients are elderly, with high incidence of dysphagia, and the doses of many anti-hypertensives range from 2.5mg -50mg. The presentation of anti-hypertensives as oral films can help improve the situation. Antihypertensive oral film is trendy, appealing and easy to administer without any need for an adjunct liquid for swallowing. Already, some researchers have prepared antihypertensives at the laboratory scale [56-58]. These manufacturing techniques as published could be scaled up to industrial levels, with an expected consequence of improved medicine adherence.

5.3. Anti-ulcers as oral films for improved adherence

The proton pump inhibitors are the drug of choice in ulcer and dyspepsia management. They have been used alongside antibiotics and antiprotozoal in *Helicobacter pylori* implicated ulcers. Omeprazole, rabeprazole, pantoprazole and esomeprazole come in strengths of between 20-40mg and can be used for as long as 8 weeks in some situations. These drugs are presented mainly as solid dosage forms of tablets and capsules, although injectibles are now available. Non-adherence could readily set in for such prolonged use coupled with swallowing difficulty. Any seeming improvement as observable by the patient could result in self-termination of therapy prematurely.

These potential and actual problems could however be overcome or at least reduced by presenting anti-ulcers as oral films. The doses and taste of the proton pump inhibitors can be effectively captured and presented in oral dissolving strips, making them appealing and trendy. Simethicone oral film is already marketed as gas-X® films while Khan *et al.*, [59] had prepared oral film of omeprazole in the laboratory.

5.4. Use of oral films in patients with dysphagia

Swallowing difficulty could be oropharyngeal or esophageal but not odynophagia nor globus sensation which does not typically make swallowing difficult [60]. Weak esophageal muscle have been implicated in dysphagia and pediatrics (neck muscle not yet fully developed) and geriatrics (failing tonicity of neck muscles) commonly present with the condition. Patients with dysphagia need to maintain a certain head and neck position to aid swallowing under the influence of gravity [https://www.cardinal health.com/en/essential- insights/coupling advanced-technology-and-human-intervention.html, Last accessed 16/12/2019.]. Such positioning can be distressing for patient who have to adhere to prescribed regimen of oral solid dosage form especially in chronic conditions of cardiovascular, diabetic or hormonal abnormalities. Exservan™, an oral film formulation of Riluzole, marketed by Zambon pharmaceuticals is useful in managing ALS patients with associated dysphagia (Table 4). When medicines used in managing ill health in patients with swallowing difficulty, are available as oral films, improved adherence becomes reachable and desired therapeutic outcomes are achievable.

5.5. Antidiabetes as Oral film improving adherence

Currently, persons with diabetes in sub-Saharan Africa, are estimated to be 20 million and the number may reach a 41.4 million by 2035 [61]. In sub-Saharan Africa, Nigeria has been pointed as having the highest number of people with diabetes with an estimated 3.9 million persons of the adult age population (20-79-year-olds) [62, 63]. Some very useful medicines for diabetes are protein insulin, the biaguanides (eg metformin) and the sulphonylureas (*e.g.,* glimepiride, glibenclamide). On the basis of dose, metformin, usually used in high dose, may not qualify for presentation as oral films, but the sulphonylureas will. Also, oral films for insulin can be incorporated using the printing method, and this will bypass the harsh conditions of the gastrointestinal tract. Pharmedica Ltd was granted in November 2018 patent for its innovative insulin oral film [63]. Bhari-Najafi *et al.,* [64] and Vaishalikilor *et al*., [44] had formulated glibenclamide and glimepiride oral strips respectively, revealing the possibility of scaling up these efforts to improve adherence to oral antidiabetics.

5.6. Formulating Anti-psychotics and anxiolytics as oral films to improve adherence

Loxapine and Clonapam are marketed antipsychotic oral films for schizophrenic anxiety and epileptic episodes respectively (Table 4). The social stigma associated with persons using medicines for conditions affecting the nervous system can be a challenge. Perceived improvement, for example, in epilepsy during the slightest seizure-free period can equally be another challenge that could, in addition, explain a possible reason for patients' non-adherence to their medication. Most drugs acting on the nervous system and for managing psychosis (usually of low dose) could be formulated as oral films [3, 13]. The trendy presentation of the dosage forms as well as its discreet use without need of adjunct liquid or public awareness is appealing and could help overcome the social stigma. These can improve adherence and result in effective therapeutic outcome. Thus, the potentials for improved adherence when antipsychotics and anxiolytics are formulated as oral films is one that pharmaceutical manufacturers can tap.

5.7. Medication for erectile dysfunction as Oral films

Erectile dysfunction (ED), although underestimated in developing countries probably because not being life threatening, is one of the most common sexual dysfunctions in men worldwide [44]. Of men aged 40-70, approximately 50% are reported to have some degree of ED. The prevalence of ED, as age-adjusted, among men attending primary care clinics were 57.4% in Nigeria, 63.6% in Egypt, and 80.8% in Pakistan [65]. Therapeutic goal is to help affected men achieve erection when necessary, restoring masculine confidence and improving relationship. Phosphodiesterase inhibitors (*e.g*., Sidenafil, Tadafil) are the medicines of choice for ED, given at a dose range of 5-100mg, and require rapid onset of action. The inertia and apprehension of taking medicines before going intimate with a mate can contribute to non-adherence of medications for ED [65]. Oral films are becoming trendy for use without unnecessary apprehension by even a sexual partner who may see them less than medicine. Low doses and intended early onset of action are additional reasons that makes these drugs qualify to be considered as oral films particularly. Several brands are currently in the market (Table 4).

Table 4 Some commercially available oral films

Drug class /therapeutic indication	Drug example and brand	Dosage form	Company	Reference
Erectile dysfunction	Sildenafil	Oral disintegrating film	Shilpa Therapeutics(New Delhi, India)	https://www.shiltherapeutics.com/products, last accessed April 02, 2020
	Tadalia® (Tadalafil)	Oral strips(20mg)	Aavishkar	https://www.aavishkar.com, Last accessed April 15, 2020
Antimigraine	Rizaport® (Rizatriptan)	Oral disintegrating film	Intelgenx	https://www.intelgenx.com, Last accessed April 15, 2020
Sedatives	Melatonin® sleep strip(melatonin &L-theanine)	Oral strips	Aavishkar	https://www.aavishkar.com, Last accessed April 15, 2020
Anti-smoking	Nicotine Cytisine	Oral Strips (1 mg /2 mg) Strips 1.5 mg	Aavishkar	https://www.aavishkar.com, Last accessed April 15, 2020

Alzheimer's disease, Parkinson's disease, stroke, high cholesterol, age-related macular degeneration	Astaxanthin Strips	Oral strips	Aavishkar	https://www.aavishkar.com, Last accessed April 15, 2020
Neurodegenerative diseases of the brain, such as mild cognitive impairment, Alzheimer's disease and dementia	Monteleukast versa film® (monteleukast)	Oral thin film	Under development by Intelgenx	https://www.intelgenx.com, Last accessed April 15, 2020
Opioid dependence disorder	Suboxone® (Buprenorphine and Naloxone)	Sublingual film	Manufactured by Aquestive Therapeutics marketed by Indivior UK	https://www.suboxone.com, Last accessed April 12, 2020
Amyotrophic Lateral Sclerosis (ALS) Somatostatins/Anti neoplastic	Exservan™ (Riluzole) Octreotide	Oral film Oral films	Manufactured by Aquestive Therapeutics but marketed by Zambon US Aquestive Therapeutics	https://www.aquestive.com, Last accessed April 21, 2020 https://www.aquestive.com, Last accessed April 21, 2020
Improve cardiac neural digestive system	Bforce® (Vitamin B12,B6, Folic acid, and biotin)	Oral strip	Aavishkar	https://www.aavishkar.com, Last accessed April 15, 2020
Analgesic and anti-inflammatory	Cannabinol Curcumin	Oral soluble film(liposomes and micelles) Oral strip	Cure Pharmaceuticals Aavishkar	https://www.curepharmaceutical.co, Last accessed April 21, 2020 https://www.aavishkar.com, Last accessed April 15, 2020
Antiepileptic	Clonapam	Oral soluble film	Aquestive Therapeutics	https://www.aquestive.com, Last accessed April 21, 2020]
Anxiety and aggression in schizophrenia and bipolar disorder,	Loxapine	Oral thin film	Intelgenx	https://www.intelgenx.com, Last accessed April 15, 2020
Antiulcer and Anti-flatulent	Simethicone 62.5mg	Oral Strips	Aavishkar	https://www.aavishkar.co, Last accessed April 15, 2020

	Gas-X® (simethicone 62.5 mg) Omeprazole	Oral thin film Buccal film	Novartis Consumer Health In the laboratory	https://www.novartis.com/consumerhealth (Last accessed 02, 2020) [59]
Antidiarrheal vaccine	Rotavirus vaccine	Oral thin film	Aridis Pharmaceuticals	https://www.grantome.com [Last accessed April 21, 2020]

6. The future of oral films in adherence

Oral films delivery is gaining grounds stealthily and rapidly as a desirable and acceptable oral solid dosage form. The current infusion of nanotechnology techniques into oral delivery opens up more opportunities for use of oral films to enhance bioavailability and in medicine adherence, adding tremendously to the relevance of this delivery system. Pharmaceutical companies are now taking advantage of these benefits of oral films and their increased acceptability, producing as films,different active pharmaceutical ingredients (APIs) to improve health outcomes. Good oral films can be achieved through a combination of proper literature search, getting feedback from patients and practitioners, and exploring the possibilities of applied advanced technology. Projecting into the future, more drugs will come into oral film product lines. With a compound growth rate of oral film market as mentioned in the outset expected to increase geometrically, the financial return on investment in this line of delivery is promising for investment [2]. Thus more classes of medications are expected to be seen presented as oral films dosage forms, contributing positively to medicine adherence.

7. Conclusion

The incorporation of nanotechnology in oral solid films has been presented with examples. This undoubtedly can improve bioavailability of medicines with good therapeutic outcomes. Also as oral films come with ease of administration, good appeal and dosage regimen simplification, medicine adherence is enhanced. As we expect more commercial quantities of oral films with incorporated nanosized drug actives, appreciating how invaluable their role would be in medicine adherence is vital and could influence prescription patterns. However, good adherence should be seen as a means of achieving a satisfactory therapeutic result and not as an end in itself.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare that, no conflict of interest is exist.

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