Oral thin films as a remedy for non-compliance in paediatric and geriatric patients

Bartholomew Yir-Erong[1], Marcel T. Bayor[*1], Isaac Ayensu[2], Stephen Y. Gbedema[1], Joshua Boateng*[*3]*

[1] Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

[2] Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

[3] School of Science, University of Greenwich, Medway Campus, Kent ME4 4TB, UK

* Correspondence: Dr Joshua Boateng (J.S.Boateng@gre.ac.uk; joshboat40@gmail.com), Prof Marcel Bayor (mtbayor.pharm@knust.edu.gh)

Keywords: Emerging technologies, drug delivery, hot melt extrusion, geriatric, paediatric, patient compliance, oral dosage forms, solvent casting, taste masking, thin films.

Abstract

Paediatric and geriatric patients experience swallowing difficulties for traditional oral dosage forms, such as tablets. Further, microbial contamination, chemical stability, unpleasant taste and swallowing large volumes of fluids have led to low therapeutic efficacy and patient non-compliance. The emergence of oral thin films has resulted in dramatic improvements in compliance and drug therapy outcomes in paediatric and geriatric patients. Oral thin films do not require water for administration, are readily hydrated upon contact with saliva, adhere to the mucosa and disintegrate ideally under one minute. This article provides an overview of oral thin films, modern trends in their formulation and characterisation, available commercial products, information to fill knowledge gaps and future potential and economic prospects of oral thin film technology, with emphasis on their use in the paediatric and geriatric patient groups.

Keywords: Drug delivery, geriatric, hot-melt extrusion, paediatric, patient compliance, oral dosage forms, solvent casting, taste masking, oral thin films,

1 OVERVIEW

The oral route remains the most widely used avenue of administering drugs aimed at achieving systemic effect, even though a few drugs are intended to dissolve in the mouth for quicker absorption or to achieve a local effect in the oral cavity [1, 2]. The oral route is the simplest, cheapest, most convenient and safest mode of administering drugs. Most clinicians and drug manufacturers prefer the oral route because of its high levels of acceptability by patients, therefore more than 50% of all the available pharmaceutical formulations are presented as oral dosage forms. Despite its wide acceptability, it is plagued by delayed onset of action, irregular drug absorption or lower bioavailability due to the first-pass metabolic effect, dysphagia, as well as the unpalatability of some active pharmaceutical ingredients (APIs) [1]. Although liquid formulations such as suspensions, emulsions and syrups are easy to swallow, they also present unique challenges; including microbial contamination, costly taste-masking requirements, chemical instability, expensive storage conditions and its bulkiness together with issues of freight which further increases cost.

Paediatric and geriatric populations are the most vulnerable patient group in terms of drug delivery and therefore, usually require special attention. The paediatric group is hugely heterogeneous comprising new-borns to adolescents with wide ranging physical and development disparities in relation to absorption, pharmacokinetics and pharmacodynamics. As the child ages, there are changes in organ function and metabolic capacity [3], particularly in early infancy. It is therefore, impossible for one formulation to fit all age sub-groups within paediatric populations, with medications used in paediatrics originally formulated for adults [4]. It is obvious that most children resist drug administration, especially oral dosage forms due to; dysphagia, nausea, vomiting, bad taste/odour or simply due to the fear of choking. The geriatric group on the other hand, comprises people aged 65 years and above. Of particular interest are those who are 75 years and older; as they may require greater attention during the design and medicine administration processes. As individuals advance in age, saliva secretion generally decreases and can result in greater difficulty to swallow capsules or tablets [3, 5]. Additionally, the ageing process predisposes patients to several health conditions, such as stroke, cancer, dementia, Parkinson's disease, and gastro-oesophageal reflux disease – and all these lead to an individual's inability to administer certain oral dosage forms (tablets and capsules) [3].

Essentially, many of the formulation challenges are common to both paediatric and the geriatric populations for either the solid or liquid oral dosage forms. In view of the aforementioned difficulties with respect to the use of the oral route for drug administration, regulators, industry and academic stakeholders have explored the development of novel oral dosage forms that assure acceptability and compliance to yield better therapeutic outcomes. The drug delivery innovations including oral thin films, that could help improve compliance in paediatric and geriatric patients have recently been reviewed [6]. These newer dosage forms, (for example, the fast-dissolving oral thin film) should offer convenience, ease of handling and administration without water, and guarantee quicker drug action, with little or no impact on lifestyle.

Several research related reports exist about oral thin films for delivering various drugs, either via pre-gastric absorption through the buccal / sublingual mucosa or following swallowing of saliva dissolved drug. However, though there are many reviews related to various aspects of oral thin film technology, its potential applications in different patient groups and their characterization, they are discussed within the context of a broader range of other dosage forms such as multi-particulates, orodispersible tablets and fixed dose combinations [130]. To the best of our knowledge, this is the first systematic review that addresses the specific application of oral thin films in two vulnerable patient groups (paediatric and geriatric). Further, it discusses in detail all the essential performance characteristics that are important for ensuring successful use by these patient groups as well as the regulatory and clinical variables that need to be considered to produce acceptable paediatric and geriatric formulations.

2 ORAL THIN FILM TECHNOLOGY

Oral thin films are sheets of flat films that are administered into the oral cavity. They are composed of very thin polymeric strips, incorporating an active pharmaceutical ingredient (API) and are intended to disintegrate in the oral cavity within seconds [7–9]. Water soluble polymers together with other ingredients are used to form the base of the film in which the active ingredient is incorporated. Oral thin films enhance the efficacy of drugs by dissolving within seconds in the oral cavity once it comes into contact with saliva and therefore do not require chewing and / or water for administration [10, 11].

Fast dissolving oral thin films are greatly accepted by patients and caregivers for their ease of delivery, accuracy in dosing and portability. Oral thin films give immediate absorption and bioavailability because of the high blood flow and permeability of the buccal mucosa and are suitable and useful in paediatric, geriatric, emetic, bedridden and mentally ill patients [13]. Even though oral thin films generally disintegrate in seconds to minutes, they can be modified to release the loaded drug more slowly depending on the film thickness and polymer matrix. By the avoidance of dysphagia and its effective taste masking potential, fast dissolving oral thin films contribute enormously to improving compliance. Fast dissolving films were first commercially made available for systemic delivery by Novartis in 2004 (Triaminic & Theraflu Thin Strips). Since then, more pharmaceutical researchers have investigated its therapeutic classes and potential markets for local and systemic delivery of drugs. As a consequence of these efforts, novel applications are evolving and are being utilised by pharmaceutical companies such as Tesa-Labtec Ltd., Germany, which became the first company ever to be granted approval for pharmaceutical oral disintegrating films.

2.1 Categories of oral thin films

Currently, oral thin films come in three different forms [14] namely;

i. Flash immediate release films
ii. Mucoadhesive melt-away films, and
iii. Mucoadhesive sustained release films

Systemic or local drug treatment can be realised using all these types of oral films and a distinction is often made between them depending on the time of disintegration and design pattern. Oral patches and mucoadhesive films are available on the market as sustained release dosage forms. For mucoadhesive or buccal films, systemic drug therapy can be achieved primarily through absorption from the oral mucosa. Furthermore, oral dissolving films are placed on the tongue whereas mucoadhesive films are placed in the cheeks though the sublingual mucosa is also a feasible route.

2.2 General attributes of fast dissolving oral thin films

Being a cutting-edge form of solid oral dosage forms, oral thin films possess unique attributes which offer significant benefits over traditional or conventional dosage forms. They are easier to administer and swallow without the need for water; ensure faster and better drug absorption into the bloodstream; combine the advantages of both solid and liquid oral dosage forms; they are more portable than syrups, capsules and tablets and therefore less expensive freight wise. Generally, oral thin films are more cost-effective than the traditional or conventional dosage forms. In addition, thin film drug delivery has the potential to allow for the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations [10, 15].

Another key attribute and advantage of these formulations is their ease of swallowing following hydration. Swallowability and taste (palatability) play essential roles in adherence to drug therapy in paediatric and geriatric patients [16]. Swallowing is a synchronised process of activities involving several nerves and muscles and safe swallowing is an ability developed by the age of twelve years [17, 18]. Liquid formulations had been the most preferred dosage form for the paediatric and geriatric populations because of dysphagia [4]. However, the emergence of fast dissolving dosage forms, especially oral thin films with taste-masking opportunities, have provided a more suitable and convenient dosing alternative for patients with swallowing challenges [17].

3 MANUFACTURE OF FAST DISSOLVING ORAL THIN FILMS

Fast dissolving oral thin films are composed fundamentally of water-soluble or hydrophilic polymers and the active ingredients [19]. The polymers normally constitute the physical structure and matrix of the film giving rise to its integrity. The chemistry behind the formulation of fast dissolving oral thin films depends on polymer science derived from the conventional solid transdermal and buccal dosage forms [20]. Taking advantage of their similarities, formulators are able to efficiently design unique products within a shorter development period [10]. In view of the flexibility in the formulation of oral thin film technology, manufacturers are able to select from a wide range of APIs and excipients for new product development initiatives. Material selection based on films' dissolution rates and rates of absorption are taken into consideration such that an equivalent or an enhanced product is developed against already existing formulations such as tablets, liquids and capsules [21] and this provides a means of extending the patent life cycle of

certain drugs for pharmaceutical companies. In addition, the oral thin film technology is being extended to cover more complicated systems for controlled or modified release including applications for topical delivery [22].

3.1 Components of fast-dissolving oral thin films

3.1.1 Active pharmaceutical ingredients

The fast-dissolving oral thin film technology has the capacity to incorporate a variety of active pharmaceutical ingredients (APIs) [23]. Oral thin films can integrate most available forms of APIs, such as micronized (most ideal), granulated, salt and free-base forms. Low dose APIs are the best molecules for the development of oral thin films. Larger particle size compounds can pose some limitations with regards to the final film's thickness and homogeneity, but generally size distributions of most drug and nutritional substances are within the classical oral thin film development requirements. Both soluble and poorly soluble drugs (Table 1) have been successfully compounded into solutions, emulsions, or dispersions that have subsequently led to the emergence of the oral thin film products currently available on the market [12]. Suitable drug candidates for fast dissolving films should be permeable through the oral mucosa, capable of taste masking, have a low dose and good stability in water and the pH should be close to that of the saliva [24] and typically make up about 1 – 25% w/w of the final formulation [9, 25].

Table 1: Oral thin films of some APIs and their solubility in water

Drug	Solubility in water	Target patient group	Reference
Piroxicam	Poorly soluble	Paediatrics and geriatrics	[26]
Tadalafil	Poorly soluble	Geriatrics	[27]
Meclizine HCl	Poorly soluble	Varied	[28]
Quinapril HCl	Freely soluble	Varied	[29]
Ketoconazole	Poorly soluble	Varied	[30]
Furosemide	Poorly soluble	Varied	[31]
Sildenafil citrate	Slightly soluble	Geriatrics	[32, 33]
Granisetron HCl	Freely soluble	Varied	[34]
Glibenclamide	Poorly soluble	Geriatrics	[35]
Chlorpheniramine Maleate	Freely soluble	Paediatric	[36, 37]
Cetirizine HCl	Freely soluble	Varied	[38, 39]
Selegiline	Freely Soluble	Parkinson's	[40]
Varsatan	Poorly soluble	Geriatrics	[41]
Loratadine	Poorly soluble	Geriatrics	[42]
Dexamethasone	Poorly soluble	Varied	[43, 44]
Tetrabenazine	Poorly soluble	Paediatrics	[45]
Carvedilol	Poorly soluble	Varied	[46]
Allopurinol	Poorly soluble	Varied	[47]
Omeprazole	Very slightly soluble	Paediatrics	[48, 49]
Clobazam	Slightly	Paediatrics	[50]
Ondansetron HCl	Poorly soluble	Paediatrics	[22, 51]
Rizatriptan benzoate	Soluble	Varied	[52]
Montelukast Sodium	soluble	Varied	[53]

Formulators can choose to develop multiple formulae to obtain manifold strengths for a specific API, or produce a single formula that is cut into multiple strengths based on the size of the unit area [10, 12]. As a result, a film of 10 mg strength can be reduced to 5 mg by dividing the unit size without further formulation efforts.

3.1.2 Film forming polymers

Water-soluble polymers are used to form the matrix of oral thin films and can be used individually or in combination depending on the desired properties of the film [12, 54]. The toughness is related

to the kind of polymer and its quantity within the formulation. The type of polymer also defines the disintegration and dissolution profile of the film as well as the other mechanical attributes, such as tensile strength, folding endurance and degree of elongation [43, 55].

Some of the polymers commonly used for formulating oral thin films include pullulan, polyvinyl alcohol (PVA), hydroxyl-propyl-methyl cellulose (HPMC), carboxymethyl cellulose, hydroxyl-propyl cellulose, sodium alginate, starch, xanthan gum and guar gum [12, 15]. In view of the vital role polymers play in the development of oral thin films, they comprise at least forty-five percent (45% w/w) of the entire film [56].

3.1.2.1 Polymer toxicity (safety)

As noted previously, the paediatric and geriatric patients are more vulnerable (in terms of normal pharmacokinetics and pharmacodynamics), than the general adult population, Further, most dosage forms administered to these populations are not specifically tailored to their unique requirements. Therefore, the safety of the dose of drug as well as the type of excipients used is of paramount importance. The polymers used must be non-toxic, non-irritant and must not contain leachable impurities. In general, most of the polymers employed are safe and in most cases already approved for use in the food, drug and cosmetic industries, and therefore are generally regarded as safe (GRAS). The polymers used can be classed into natural such as pullulan, pectin, carrageenan and synthetic such as Carbopol, cross carmellose sodium and PVA depending on need and availability [11, 57, 58]. Khan and co-workers tested the cytotoxicity of Metolose (HPMC) based films containing omeprazole for buccal delivery to paediatric patients using MTT assay and showed to be safe for use in children [49].

The application of certain polymers imparts specific properties to the final formulation. For example, gelatines come in different molecular weights which can impart aesthetic and glossy features to films [54, 59]. Pullulan is also regularly employed to produce films with good solubility, mechanical strength and stability at varied temperatures [54]. In the formulation of triclosan, different grades of HPMC (Methocel E3, Methocel E5 and Methocel E15 premium LV) were used as polymers and the result showed that Methocel E5 at 2.2%w/v yielded films with excellent properties. In addition, granisetron hydrochloride was developed using HPMC and pullulan and the outcome demonstrated the importance of increasing polymer concentration on

physical and mechanical properties. Films from pullulan at 40 – 45% did not exhibit good mechanical strength while HPMC at a concentration of 40% formed a film that was difficult to remove. However, the film stickiness became better when the HPMC concentrations were increased above 50% [34].

Even though polymers are commonly used excipients, they have emerged as vital components in the development and formulation of fast dissolving oral thin films. Therefore, a fundamental knowledge and understanding of the properties – chemistry, rheology, and physico-chemical behaviour of polymers is essential to successfully develop effective oral thin films. It is crucial to choose the appropriate polymer that will produce thin films with properties that will assure therapeutic success [60].

3.1.3 Plasticizers

Generally, plasticizers influence the mechanical properties, such as tensile strength, elastic modulus and percent elongation of oral thin films and therefore, its choice and amount should be properly taken into consideration [60]. They are vital to obtaining the desired film flexibility [61] and act by lowering the glass transition temperature of the films resulting in improved film plasticity and elasticity [62]. Some of the commonly used plasticizers include polyethylene glycol, propylene glycol, glycerol, sorbitol (also a sweetener), phthalates, low-molecular-weight macrogols, and citrates [7]. Water is still present in the dried films and can act as a plasticizer in synergy with any of the plasticizers mentioned above. Plasticizers at high concentrations may cause impairment of moisture resistance giving rise to tacky films or stability challenges. Drug solubility and absorption can also be affected by the addition of plasticizers [7, 63] and therefore the concentration of plasticizer relative to the polymer content needs to be optimised.

3.1.4 Surfactants

Surfactants (or surface active agents) are micro-molecules which adsorb at surfaces and lower the interfacial tension. Surfactants work as wetting or solubilizing agents in oral thin films and help in ensuring that the films disintegrate within seconds to release the API [64, 65]. Commonly used surfactants in thin film formulations include poloxamer, sodium dodecyl sulphate, benzalkonium chloride, sodium lauryl sulphate and polysorbates (tweens) [66].

3.1.5 Saliva stimulating agents

Films are intended for fast disintegration in the mouth and mainly dependent on the presence and quantity of saliva. It is therefore vital to introduce saliva stimulating agents in the formulation of fast dissolving oral thin films to increase saliva production rates [67]. Acids used in the food industry are commonly utilised as saliva stimulating agents and these include citric (most preferred), lactic, ascorbic, malic and tartaric acids [9, 68]. Saliva stimulants are used alone or combined to achieve the desired effect and these typically form about 2 – 6% w/w of the entire oral film.

3.1.6 Colouring agents

A full range of natural colouring agents and juice concentrates are approved and available for incorporation in the formulation of oral thin films [54]. These include FD & C natural colouring agents and pigments such as silicon, zinc and titanium dioxides. The concentration of colouring agents in oral thin films do not exceed 1% w/w [9].

3.1.7 Taste masking (sweetening and flavouring) agents

Many drugs are bitter in their natural form and even drugs that are only partially soluble in saliva are accessed by the taste buds. Therefore, it is essential for taste-masking agents to be incorporated into fast dissolving films. Depending on the physical state of the drug in the film and its solubility profile in saliva, various taste-masking techniques are available for application [69].

Taste masking additives include sweeteners and flavours that are capable of disguising the unpleasant taste of drugs [70, 71]. Using a combination of sweeteners and flavours to overcome an unpleasant taste is the most common approach in taste masking [72]. Other more sophisticated methods such as particle coating, and complexation with ion exchange resins are used. Several sweetening agents exist in both natural and synthetic forms and typical sweeteners include fructose, glucose, maltose, galactose, sucrose, dextrose, isomaltose, xylose and ribose [55]. Others are mannitol, aspartame, sucralose, neotame, sodium saccharin, acesulfame-K, xylitol, and sorbitol. Some sweeteners are sweeter than others; for example, fructose is sweeter than sorbitol and mannitol; acesulfame-K and sucralose have respective sweetness values of more than 200 and

600 times that of fructose. Others such as mannitol and xylitol provide good mouthfeel and cooling sensations in the mouth [34]. First generation artificial sweeteners are saccharin, cyclamate and aspartame, whiles acesulfame-K, sucralose, alitame and neotame are the second generation of synthetic sweeteners. Typically, different combinations of sweeteners and flavours are employed to achieve the desired taste-masking effect. For example, citric acid and passion fruit flavour were found to be suitable for complete taste-masking of cetirizine HCl [39].

Flavours help to improve the acceptance of drug formulations by attempting to conceal unpleasant smell. Therefore, both natural and synthetic flavours are employed to mask such APIs and improve the organoleptic indices of oral thin films. The acceptance of flavours is affected by ethnicity and the age of the patients. Paediatric patients like fruity flavours e.g. raspberry and punch, whiles geriatric patients tend to prefer mint flavours e.g. orange [54]. Importantly, the amount of flavour that can be incorporated depends on the API, the flavour type and its strength. Generally, about 10% w/w concentrations of flavours are added to formulate fast dissolving thin films. Examples include the synthetic categories (oleoresins, peppermint oils, cinnamon oils and spearmint oils) and fruity flavours (vanilla, cocoa, coffee, mango, chocolate and fruit essences such as cherry, raspberry, apple and pineapple among others). These flavours can be used individually or in combination [19, 59, 73].

3.1.8 Permeation enhancers (for mucoadhesive films)

Though fast dissolving oral thin films are typically placed on the tongue for rapid dissolution and swallowing, multipurpose oral thin films are increasingly being employed for initial buccal absorption and subsequent dissolution and eventual swallowing of the remaining free flowing gels, containing unabsorbed drug. A typical example is NiQuitin oral thin films for nicotine replacement therapy to aid smoking cessation [74]. This therefore requires use of permeation enhancers to improve the initial absorption of drugs into the systemic circulation [58]. Permeation enhancers are added to increase the permeation of the drug molecule across the membrane, thereby aiding buccal and sublingual absorption [20]. Commonly used permeation enhancers are dextran sulphate, cyclodextrin, menthol, sodium deoxycholate, aprotinin, benzalkonium chloride, lauric acid and oleic acid [75]. It has also been proposed that permeation enhancers improve mucosal transport via changing the mucus rheology by reducing the viscosity of the mucus layer,

modification of drug solubility parameters and facilitating transport by way of increasing the membrane fluidity [76, 77].

3.1.9 Thickening agents

Film stabilizers and thickening agents are incorporated to enhance the viscosity and uniformity of the solution or suspension prior to casting [54]. For example, in the development of oral polymer films containing loperamide, Woertz and co-workers demonstrated that the content uniformity increased when thickening agents were added [78]. Non-artificial gums such as xanthan, guar and locust bean gums, carrageenan and cellulosic derivatives can be used at concentrations of up to 5% w/w. Other additives such as suspending and emulsifying agents may also be added in small quantities to enhance the properties of the films [79].

3.2 Patient-centred considerations for formulation of fast dissolving oral thin films

3.2.1 Acceptance

Dosage form acceptance by patients is essential to its compliance. Problems usually encountered in the use of conventional dosage forms such as dysphagia can be overcome by oromucosal formulations [80]. Though crushing of traditional oral dosage forms to make it easier to swallow could help, it may affect performance indicators such as dissolution and absorption rates of the drug [81]. Though orodispersible tablets can also improve swallowing in dysphagia, issues of aspiration still persist [18]. The use of liquid formulations to ease swallowing problems is fraught with challenges including dosing inaccuracy, drug instability and unpalatability. With the advantage of a fixed dose and ease of administration without water, adequately formulated oral thin films can address all the problems of other oral dosage forms leading to high levels of acceptability.

In an acceptability study with 19 patients, dexamethasone oral thin film showed superiority in terms of taste and ease of administration compared to a tablet [43]. Therefore, in the formulation of oral thin films, it is imperative to consider as essential, acceptance issues such as taste, mouthfeel and mucosal irritability; which may appear less important for capsules, tablets or liquids. However, it is important to note that a dosage form that is ‘too acceptable’ could be

susceptible to drug misuse, especially in paediatric populations and must be strictly kept away from the reach of children [80].

3.2.2 Excipients

Practically, most of the excipients used in the formulation of fast dissolving oral thin films have been used in one dosage form or the other either as polymer matrices or coating materials. These excipients have to be evaluated for the quantity required, in view of age appropriateness and acceptable daily intake [4]. Residual solvent assessment is necessary if organic solvents are used in the development of oral thin films by solvent casting. This is because organic solvents are hazardous and therefore, should not exceed the daily acceptable intake and this is usually specified in standard regulatory quality documents such as United States and British Pharmacopoeias [13, 82].

On regulatory requirements, it is essential to justify the use of an excipient in the formulation, especially if the product is meant to be delivered to the paediatric population [83]. As a result, the European Medicines Agency (EMA) recommends in its guidelines, specific requirements for the development of medicinal products for children, pointing out the need for safety data on the excipients used [84]. It is therefore prudent to incorporate excipients that have been tested and approved for use in other dosage forms to shorten the development and safety evaluation processes. However, according to Pries and co-workers, approaches with new substances, such as those able to mask bitter taste appear hopeful but may increase the regulatory requirements [85].

3.2.3 Appearance

The appearance of a dosage form including oral thin films is vital to achieving compliance by patients [86]. Even though the appearance of oral thin films may differ, they should generally be smooth, soft, flexible and free of air bubbles [81]. However, dosage forms in which the colour is associated with sweetness are capable of drug misuse, particularly in children and therefore requires caution, with appropriate labelling and storage. By using different polymers, it is possible to improve the appearance of oral thin films as well as prevent the recrystallization of APIs during

storage to maintain the physical aesthetics and visual appeal of the dosage form. Polymers such as HPMC, polyvinyl pyrrolidone and methylcellulose are known recrystallization inhibitors [23].

3.2.4 Taste and palatability

Taste plays an important role in the acceptability of a dosage form, and since oral thin films are intended to disintegrate in the mouth, there would be an unavoidable interaction with the taste receptors [19]. Dosage forms and or APIs with unpleasant taste may lead to non-compliance by the patients [4, 87] and therefore an effective approach to mask the unpleasant taste is necessary. Probably, the cheapest approach to mask the bitter taste of APIs is the incorporation of flavours, sugar alcohols and artificial or nutritive sweeteners; or a combination of these excipients [88]. Several attempts have been made to mask the bitter taste of some drugs as reported in the literature. For instance, an oral thin film containing cetirizine hydrochloride was deemed to have masked the bitterness of the API by the application of sweeteners and other taste masking agents [38, 39]. Taste-masking evaluation is carried out to determine the efficiency of the chosen approach. Human taste panels and electronic tongues are employed depending on the availability and suitability, to appraise the palatability of various developed formulations including oral thin films [55].

3.2.5 Mouthfeel

Unlike the conventional solid oral dosage forms in which ingestion is critical, oral thin films, disintegrate in the mouth and remain there for a relatively longer period. As a result, texture and mouthfeel, as well as size considerations, have to be provided for in the development of oral thin or fast dissolving films [81]. The relatively small space of the oral cavity available for drug application limits the size of oral thin films. Reported studies adjudged formulations with film area of 4 cm^2 and a thickness of 0.10 mm [59] as well as 6 cm^2 and thickness of 0.35 mm [89] as being acceptable for oral application. On the other hand, film with areas of 1 cm^2 and 2 cm^2 were evaluated as acceptable for mucoadhesive films [90]. A major difference between mucoadhesive and fast dissolving films lies in their behaviour in the mouth, and hence the texture has to be estimated. For fast dissolving films, the texture following disintegration needs consideration since remnant particles may negatively affect the mouthfeel and its resultant influence on the acceptability of the films. An unpleasant mouthfeel may be inevitable if the film is gummy after

wetting; because of viscous polymer behaviour [81]. Excipients such as polyacrylic alcohols (PAA) are capable of improving mouthfeel due to their cooling effect [66]. In the case of mucoadhesive films, texture following disintegration is less important and features of functional importance include adhesiveness, flexibility, and change in the residence time within the oral cavity [90].

4 METHODS OF MANUFACTURING FAST DISSOLVING ORAL THIN FILMS

Methods used in the development of fast dissolving films include solvent casting, hot melt extrusion (HME), semisolid casting, solid dispersion extrusion and rolling [81, 90]. These methods can be used individually or in combination, but solvent casting and HME are the most commonly employed methods [85].

4.1 Solvent casting

Solving casting is the most widely used method for the manufacture of fast dissolving oral thin films [66]. Hydrophilic polymers together with other water-soluble ingredients are used as film formers. The solvent chosen is usually on the basis of the solubility of the API. The film-forming polymers are usually dissolved in a solvent, either in water only or in combinations of water and organic solvents and the other excipients are then added to form a homogenous solution [20]. Several papers have been published in which solvent casting was used to obtain films for paediatric or geriatric applications. For example, Mahmood and co-workers [36], and Teja and co-workers [37] successfully formulated chlorpheniramine maleate oral thin film for paediatric application to aid swallowability as well as improve therapeutic effectiveness using the solvent casting method. Bonsu and colleagues reported the application of solvent casting to develop diclofenac sodium oral thin film for the treatment of osteoarthritis in older adults [91]. Similarly, furosemide oral thin film aimed at improving the solubility of the API was formulated using solvent casting [31].

Organic solvents are capable of improving the solubility of the API and reducing the drying time. Once the polymer matrix is formed, the API is added, typically pre-dissolved or pre-dispersed in an aqueous medium. Removal of any entrapped air bubbles is mandatory before casting is done; as this is essential to obtaining uniformity of film properties [66]. Specific types of equipment such as rollers (Figure 1) are required for pouring the solution on an inert base and the space between

the roller and the substrate determines the required thickness of the film. Once the casting is undertaken on a suitable platform (substrate), it is allowed to dry, preferably in hot aired oven or by convection [92]. When sufficient dryness is achieved, the film is gently removed or peeled off and cut into suitable sizes and shapes with respect to the intended dosage of the API. Although in industry, the films are sometimes rolled (known as "roll stock") and stored, until a later date before cutting, it is really ideal to cut and package it soon after preparation to maintain its stability and integrity. The packaging materials of thin films are meant to render adequate mechanical strength to protect the film against humidity and temperature [4]. In view of the film characteristics, single unit or multi-unit dispensers are chosen.

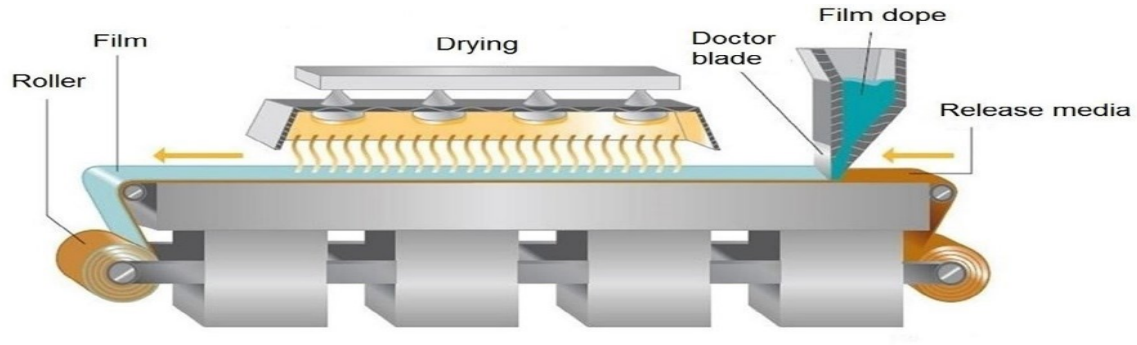

Figure 1: Equipment for the commercial processing of oral thin films by solvent casting (Reproduced from Amin et al [61] under Creative Commons Attribution 4.0 International License).

4.1.1 Advantages of solvent casting

There are several benefits associated with films produced by a solvent casting method. Solvent casting is ideal for the development of oral thin films incorporating heat-sensitive APIs. This is because the temperature required to achieve dryness is relatively low in comparison to those of HME [10, 93]. In addition, oral thin films produced by solvent casting have better physical properties, excellent homogeneity of thickness and weight, as well as easy and low cost of manufacture and processing [61].

4.1.2 Disadvantages of solvent casting

In spite of the usefulness of solvent casting for producing oral thin films, it is associated with some limitations. Solvent cast films may contain traces of residual solvents which are mostly organic in

nature and can be hazardous to patients and the environment and for this reason, many countries have adopted regulations governing the use of organic solvents [10, 18]. The manufacture of oral films on a large scale is problematic, as heating, temperature and mixing rates could introduce variability in the uniformity and quality of the final films [93]. It would require a huge investment to optimise the production units such as mixing rates, drying time and film thickness and this may affect the scale of commercial production [20]. Films developed by solvent casting are liable to brittleness upon storage shown by reduction in percent elongation as a result of evaporation of the residual water over time.

4.2 Hot melt extrusion (HME)

HME is an innovative drug delivery technology that has received intense attention from both the pharmaceutical industry and the academic research community [94, 95]. HME was first made available in the plastics industry and in its elementary form, it compacts, blends, grinds and kneads powder or solid mixtures into uniform products for further processing into different formulations (Figure 2).

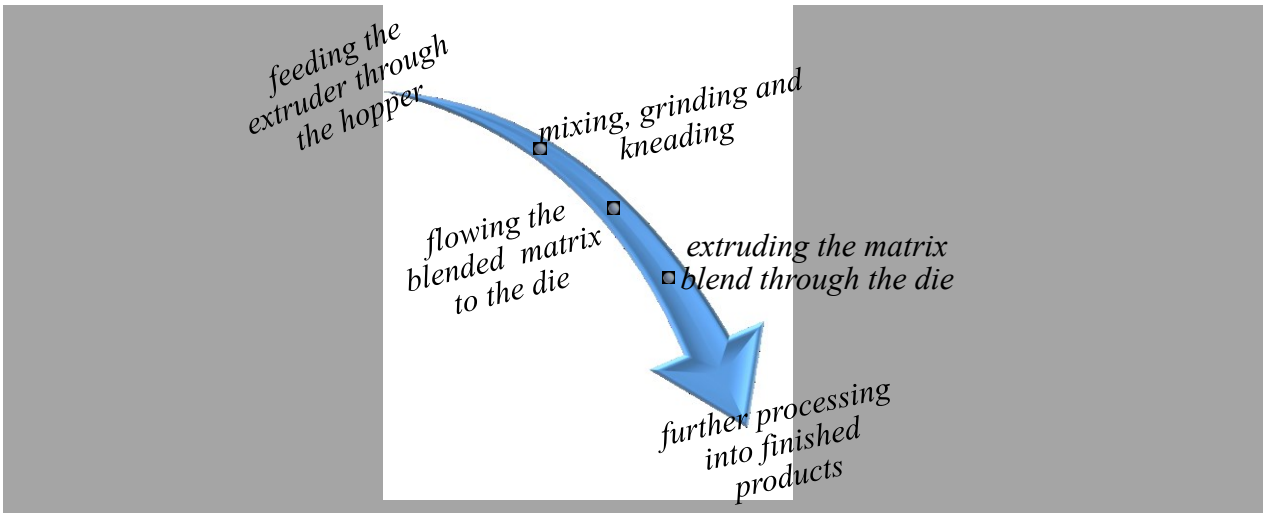

Figure 2: The hot melt extrusion process

Hot melt extrusion is a solvent-free process which involves the use of heat to form the films unlike in the solvent casting method. The excipients and the API are heated and homogenised by a screw extruder until they are fully blended. The blend is passed through a flat extrusion die which presses the extrudate into the desired film shape, cooled and cut to the required size and packaged [96].

The main components of the HME equipment are the hopper, extruder, film die and the roller. The extruder also has one or two rotating screws in a static cylinder barrel as shown in Figure 3.

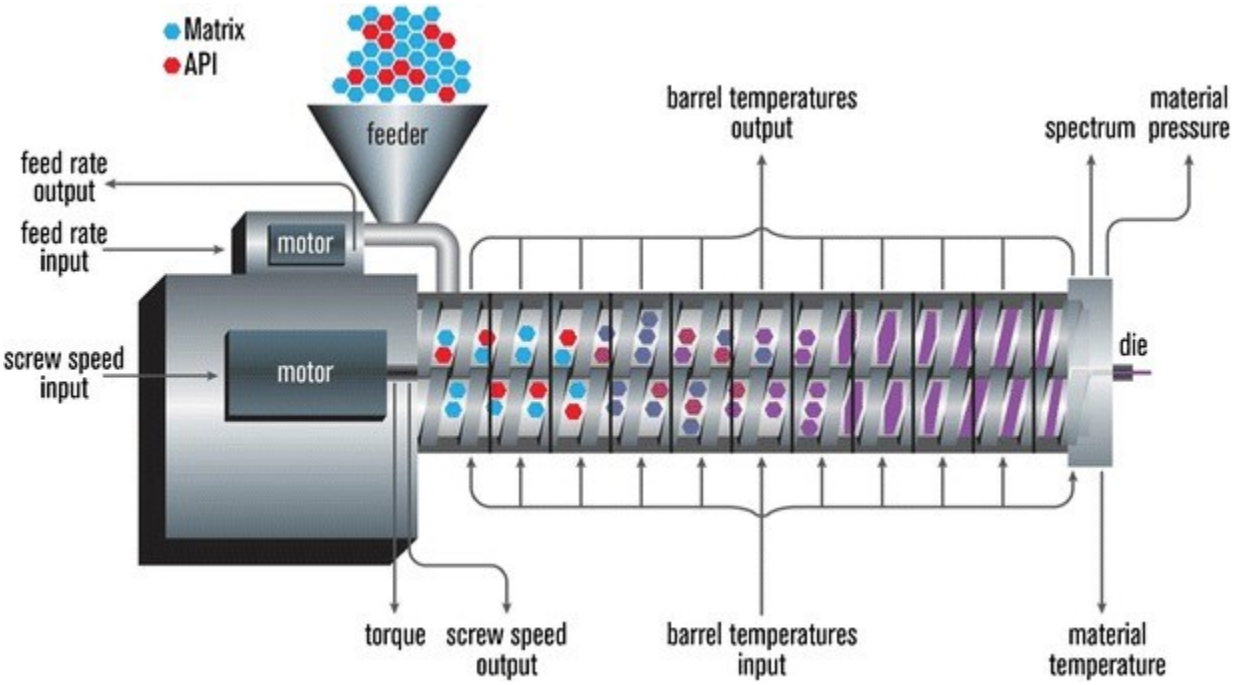

Figure 3: Hot melt extrusion equipment (Reproduced with permission) [129]

HME is a versatile method that has achieved considerable success in academic research and the pharmaceutical industry for its role in drug delivery via oral, transdermal and transmucosal routes in the form of tablets, films, capsules, implants, granules and pellets. It is also effective for the masking of the unpleasant taste of pharmaceutical ingredients thereby improving compliance [97, 98]. In a study to evaluate the *in vivo* and *in vitro* taste masking efficiency of hot melt extruded paracetamol formulations, a panel of six healthy volunteers appraised the formulations to be effective and the rating was consistent with the electronic tongue results of the same formulations [99]. Similarly, fast dissolving chlorpheniramine maleate films were developed by HME and the results of the taste masking demonstrated that the method used had reduced the bitterness of the drug in the film relative to the pure drug and physical mixtures [100]. In another study, Manirruzaman and co-workers designed oral thin films of ketoconazole produced by HME which showed more rapid drug dissolution compared to the pure drug [30].

4.2.1 Advantages of HME

HME has several unique advantages over other manufacturing techniques for producing orally administered solid dosage forms [94, 96, 101, 102]. There are fewer processing steps and therefore produces films and other formulations quickly, which saves time. It is an anhydrous and solvent free process and therefore does not require water or other solvents, and hence eliminates problems associated with drug instability as well as issues of residual solvents. It is also proven to be environmentally friendly because of the avoidance of organic solvents. There is a homogeneous dispersion of fine particles in view of the agitated mixing and films produced by HME therefore have the potential of improving the solubility of poorly soluble drugs.

4.2.2 Disadvantages of HME

The major drawback of HME is the negative impact of the high temperatures (thermal degradation) on APIs and other ingredients, especially those which are thermo labile [63]. All the ingredients used in HME must be free from water or other solvents; otherwise, the heat applied during processing can cause it to boil and evaporate thereby creating voids in the final film product which can affect its uniformity, appearance and strength. The rheology of the polymers is essential to the processing of the films by HME, therefore the number of polymers that can be easily processed is limited [95, 96, 101].

5 REGULATORY REQUIREMENTS OF FAST DISSOLVING ORAL THIN FILMS

Pharmacopoeias such as Ph. Eur., USP, and BP, provide monographs of common dosage forms. Dosage forms administered orally such as orodispersible tablets, medicated chewing gums, oro-mucosal preparations, and lyophilisates are included but monographs and specifications for oral thin films of various dissolution profiles are yet to be established [103]. In addition, there are inadequacies in the pharmaceutical technical procedures for analysis and quality control of oral films. For example, though the disintegration and dissolution analytical procedures may be available, the recommended conditions such as volumes of dissolution media do not reflect the natural conditions in the oral cavity [103]. Although the EMA and FDA have recently provided guidelines for industry, especially in development of formulations for vulnerable patient groups such as paediatric and geriatric populations, more research is required to establish global standards

since most of the reported studies vary greatly in the methodology and approaches, and it is difficult to tell which is appropriate.

5.1 Characterisation and quality control of fast dissolving oral thin films

In view of the novelty of fast dissolving films, it is expected that these films would be flexible, soft, elastic, palatable as well as physico-chemically stable. Therefore, several quality control attributes are usually evaluated. Some of these parameters are considered carefully in the design and development stages of the oral thin films and are thus, not tested at the end of manufacturing process. Characterisation of fast dissolving oral thin films is a fundamental undertaking and includes the assessment of parameters such as *in vitro* formulation disintegration and drug dissolution, uniformity of weight and thickness, folding endurance, tensile (mechanical) strength, , percent elongation, Young's modulus, moisture content, assay of drug content and swelling properties among others [104]. The following are some of the various essential quality attributes that define optimised oral thin films.

5.1.1 Surface pH

Irritation may occur in the oral mucosa if the film is too acidic and therefore it is necessary to determine the surface pH of the films. Because it is intended to disintegrate in the mouth the pH of the films should be close to the pH of saliva, neutral pH values or values close to 7 are ideal [22]. The films are made to hydrate in small volumes of water, simulating absorption of saliva and the pH values are recorded using a pH meter [56]. The surface pH of the films can also be estimated by using pH paper. The film is placed on 1.5% w/v of agar gel, allowed to hydrate and the pH paper is then brought into contact with the swollen film and any colour change is noted and interpreted appropriately [56, 105].

5.1.2 *In-vitro* disintegration

Oral thin films are designed to disintegrate in the mouth and disintegration tests are therefore performed to determine the time taken for a film to split or break up when it comes into contact with saliva or dissolution medium. Assessment of disintegration is usually based on visual inspection where the film is placed in water (25 ml) or any appropriate medium and monitored

until it breaks into pieces. The United States Pharmacopoeia (USP) disintegration apparatus can also be used to study the disintegration time. The ideal disintegration time for fast dissolving oral thin films is between 5 – 30 seconds [9, 54], though disintegration within 60 seconds is acceptable. Disintegration has been modelled using various approaches including measuring contact angle and analysing swelling behaviour of the oral thin films. In addition, other approaches including slide frame the Petri dish protocols have been reported and these tests deal use a small volume of disintegration medium simulating the small volume of saliva in the mouth. Mishra and Amin placed films on a stainless steel wire mesh containing 10 ml of distilled water and the disintegration time was recorded as the time taken till the film broke [38, 39]. In another test, disintegration was evaluated in a glass dish with 25 ml distilled water. The dish was swirled intermittently and the time taken for the film to start breaking recorded. Hydration of films was measured in a diffusion apparatus [106]. Although the above approaches can allow the distinguishing of different oral thin films they do not sufficiently mimic the physiological conditions in the oral cavity, since the mastication action of the tongue on the oral thin films is not accurately replicated. Mostly, distilled water is used as the disintegration medium and there is no simulated saliva described in the various Pharmacopoeia, though some researchers have reported disintegration using simulated saliva [49].

5.1.3 Swelling index

Polymers used for developing oral thin films are hydrophilic and therefore, it is necessary to study their swelling behaviour [107]. This is however, more applicable for swelling controlled release bioadhesive systems, compared to rapid release systems which are meant to disintegrate or dissolve very quickly within a few minutes. Swelling of polymeric films is a fundamental function of bioadhesion [108] and the extent and rate of swelling are also essential in controlling how much of the drug is released [106, 109]. Hydrophilic polymers with dissimilar structures possess varying degrees of swelling based on the relative resistance of the matrix network structure to the movement of water molecules**.** For example, a polymer chain with low ability to form hydrogen bonds is incapable of forming a strong network structure, and water penetration is difficult to occur [59]. Once the number of hydrogen bonds, as well as the strength of the polymers, increase, the diffusion of water molecules into the hydrated matrix occurs at a slow rate [110]. Panomsuk [111] discovered that the introduction of mannitol into methylcellulose films decreased the swelling

index of the resulting matrix which may have resulted from hydrogen bonding between the drugs and polymeric matrix.

Swelling index studies are estimated using various simulated fluids; where the sample is usually weighed and placed in a previously determined stainless steel wire mesh or sieve [112]. The wire meshes together with film are then submerged into a sufficient volume (ideally 20 ml or more) of the simulated fluid in a beaker. The excess water on the surface of the film is removed by the aid of a filter paper prior to reweighing. The increase in the film weight is determined at regular time intervals until a constant weight is obtained. Mathematically, the degree of increase or swelling is calculated using the equation below:

$$\textbf{\textit{Swelling index}} = \frac{\boldsymbol{Wt - Wo}}{\boldsymbol{Wo}},$$

where; Wt is weight of film at time = t, and Wo is weight of the film at time 0. It can be expressed as a percentage.

5.1.4 *In-vitro* dissolution

There are various means of determining the dissolution of fast dissolving oral thin films. Commonly, the USP dissolution apparatus is used with various modifications as is practically possible. Individual films are used in the dissolution test and an aliquot is withdrawn periodically, suitably timed and the dissolution medium is replaced accordingly [51, 54, 113]. The solutions obtained are analysed using UV spectrophotometer or HPLC at specific wavelengths. Further, the basket or paddle method specified in any of the pharmacopoeias can be adopted. However, it can be difficult using the paddle method for fast dissolving oral films dissolution test because the films are more likely to float on the surface of the dissolution media.

5.1.5 Thickness

Uniformity of thickness is essential to obtaining accuracy of a dose of oral thin films. A film that has suitable thickness assures the comfort of administration and the acceptable thickness of typical oral thin films is typically 50 - 1000μm. The film thickness is commonly measured with a micrometre screw gauge, Vernier callipers or scanning electron microscopy images [15, 114] and normally measured at 4 different locations of the films and the mean value estimated [59, 107].

5.1.6 Moisture content

The moisture content has a critical effect on the mechanical strength, adhesiveness, and friability of films [115]. Many factors account for the high amount of moisture, including; hygroscopic properties of API, polymers, plasticizers, solvent system used to dissolve the polymeric mixture, and manufacturing techniques. In general, the moisture content of the film is determined by methods such as Karl Fischer titration or thermogravimetric analysis (TGA) [13]. In TGA, pre-weighed films are heated to temperatures of 100 – 120 °C until they attain constant weight. The relation below is then applied in estimating the amount of moisture in the film, expressed as a percentage [59].

$$Moisture\ content = \frac{initial\ weight - final\ weight}{initial\ weight} * 100$$

5.1.7 Uniformity of weight

When the films are dried, removed and cut into desirable sizes, the weight of individual films is estimated. The manufacturing method is effective if the weight variation is low as this would indicate uniformity of content [116]. Fundamentally, the weight variation is estimated to ensure that the films comply with uniformity of content of the API and thereby ensuring accuracy in dosing [12, 20].

5.1.8 Surface morphology

Scanning electron microscopy is an essential tool with a variety of applications. It is used to obtain morphological, topographical and compositional information of solid materials and can also detect and analyse surface structures, examine surface contaminations, obtain information in microstructures, and reveal spatial variations in chemical substances [48, 106, 117]. It is also used to obtain images of oral films displaying the various units in the films and as a result, the spatial variations of the drugs and excipients in the film [21, 109, 118].

5.1.9 Mechanical Properties

Tensile strength

Generally, the mechanical strength is characterised by its tensile strength, which is related to the stretching ability of the film [54, 91]. The mechanical strength is measured by instruments such as texture analyser or Instron tensile tester, in which the film is held between two clamps and pulled to determine the tensile strength by noting the force or stress at which it breaks into two parts. Tensile strength is then, determined by the formula; $\sigma TS = \frac{Fmax}{A}$; where: σTS is the tensile strength, Fmax is the load (force) at break and *A* is the initial cross-sectional area [105].

Folding endurance

This is evaluated by folding the film at the same place repeatedly at an angle of 180° until the film breaks [55, 103] and is an indirect measure of flexibility. The number of times the film is folded till the breakage is the folding endurance [119]. It is important for oral thin films to have a good folding endurance in order to maintain the dose integrity. Films with folding endurance value of 300 or more is considered to be ideal [120].

Young's Modulus

Young's modulus refers to the elasticity or stiffness of the oral thin films. It is the resistance to deformation of the films and can be estimated by plotting stress and strain curve, where the slope represents the modulus [67] and the greater the slope, the better the tensile modulus and deformation and vice versa [95]. A film that shows higher tensile strength and greater Young's modulus is hard and brittle with small elongation.

Young's modulus = $\frac{\textbf{slope x 100}}{\textbf{film thickness x cross}-\textbf{headspeed}}$

Percent elongation (elongation at break)

Elongation is a deformation, characteristically, a change in shape of an object when stress is applied and is measured to obtain a predictive value of ductility of the polymers used. Percent elongation shows the stretching ability of the material without breaking whiles elongation at break indicates the point at which the film can be stretched when is broken by the applied stress [64]. All kinds of elastomers exhibit the elastic elongation phenomenon. When stress is applied to a sample, the strain is generated, and the sample elongations will become more predominant as the amount

of stress applied increases [56]. Upon reaching a certain limit, the sample breaks; this point of breakage is referred to as percent elongation break. The relation below can be used for estimating percent elongation [54].

$$\textbf{\% elongation} = \frac{\textbf{increase in length of film x 100}}{\textbf{initial length of film}}$$

5.1.10 Assessment of taste masking efficiency and organoleptic indices

Taste and palatability play important roles in the acceptability of medicines by patients [121, 122]. Therefore, taste is a critical feature of oral thin films and taste masking is essential for unpleasant or bitter drugs to enhance patient compliance, especially in the geriatric and paediatric populations [123]. Various means of assessing taste-masking efficiencies are available. The use of taste panel is an option where human volunteers evaluate the organoleptic indices of the films and values are recorded in levels of acceptability [5, 72]. There are arguments of lack of objectivity in using human taste panels [81] especially for formulations meant for paediatric use; based on the principle that taste preference is age and ethnicity dependent [5]. However, though the human taste panel has limitations, it is the only realistic means by which levels of acceptability of grittiness and good mouth-feel can be assessed and therefore very difficult to entirely eliminate from the essential quality assessments [87].

There is also innovative *in vitro* approaches in which taste is assessed electronically, using the electronic tongue [121]. For example, commercially available electronic taste system by Insent (Astugi-Shi, Japan) and AlphaMos (Toulouse, France) determine human taste attributes such as sweetness, saltiness, bitterness, sourness and astringency [124]. The measurement principle is based on its sensitivity to different ionic molecules. Together with the ability of the sensors to bind or interact with different chemical structures, they allow an estimation of the overall impression rather than only the determination of the concentration of the API [99].

5.1.11 Pharmacokinetic profile

Oral thin films generally employ water soluble polymers which allows the dosage form to be quickly hydrated by saliva, adhere to the mucosa, and disintegrate within a few seconds, dissolve and release the API for mucosal absorption when placed on the tongue or in the oral cavity. The

sublingual mucosa having a thin membrane and large veins is readily permeable, which gives instantaneous bioavailability of drugs due to rapid blood flow [54]. Pre-gastric absorption can also improve bioavailability by bypassing the hepatic first-pass effect with consequent reduction of dosage and unwanted effects [11].

Though oral thin films are effective formulations for oral drug delivery, they have certain limitations including poor ability to load drug and dependence of the drug release physico-chemical characteristics of the target drug, for example its aqueous solubility. As a result, controlling the rate of drug release from oral thin films is difficult, though can be achieved through modification of the polymer matrix [51, 113]. Consequently, oral thin films are appropriate as single dose immediate release products. Therefore, the plasma pharmacokinetics, relative bioavailability and safety profile of the drugs in oral thin films need to be established as superior alternative to the traditional tablets and capsules [60]. This is primarily achieved by comparing the *in vivo* rate (peak plasma concentration; C_{max}) and extent (area under the curve [AUC] from administration to last observed concentration time; AUC_{0-t}) of drug absorption after single-dose administration of the test and reference drugs in human volunteers [2, 32, 125].

6 PACKAGING AND STORAGE OF FAST DISSOLVING ORAL THIN FILMS

Oral thin films are moisture sensitive and therefore require special packaging techniques which are essential to provide mechanical protection and maintain the stability of the films. The packaging materials act as barriers to the penetration of moisture, air (oxygen) and light. Packaging is also important to ensure easy handling and transport from one place to another. Aluminium foils are regularly used in the packaging of thin films as these are considered to be the most ideal for maintaining the integrity of the films [19]. Lidding foils are also reported to be used for the packaging, especially if tamper proof is required. The packaging of oral thin films has usually been done in single unit dosage formats that contain one or two films for each pouch and enables portability of the product [12]. It also allows for multiple-count options to accommodate dispensing needs and regional requirements. Films are made available in both single and multi-unit dose blisters; though single dose packaging is often preferred to avoid accidental overdosing should the films stick together. Once the films are packaged it is

thoroughly examined before placing into the secondary container. Pocketpaks™ for cool mint Listerine has been introduced by Pfizer [10, 59], while a patented packaging system - Rapid card for Rapid® films (APR-Labtec GmbH) [14, 125], which has the same size as a credit card with three films on each side, is individually removable.

7 COMMERCIAL FAST DISSOLVING FILM TECHNOLOGIES

7.1 Soluleaves™

Soluleaves™ [5, 54, 81], films are designed to dissolve fast once in contact with saliva, releasing the active ingredients and flavours quickly. The delivery system can be used for a wide range of therapeutic areas and nutritional products. This method is particularly useful for paediatric and geriatric patients who may have difficulty swallowing traditional tablets or capsules as previously noted in this review. Soluleaves™ films can also be formulated to stick to the mucous membranes and to release the active ingredients gradually over 15 minutes.

7.2 WaferTab™

WaferTab™ combines pharmaceutical actives into an ingestible oral thin film. The system offers rapid dissolution and release of actives when there is contact with saliva in the mouth. The film produced can be flavoured for additional improvement in palatability [66, 92]. The WaferTab™ system is versatile and can be adopted in innovative ways of drug design, and facilitating multiple films with different actives to be bonded together.

7.3 XGEL™

XGEL™ is a Meldex trademark which it uses in all its film delivery systems and ingestible formulation technologies [34, 92, 126]. XGEL™ film delivers distinctive product benefits for healthcare and pharmaceutical products and is non-animal derived.

7.4 Foamburst™

Foamburst™ is a special modification of the Soluleaves™ technology in which an inert gas is injected into the film in the production stage [34, 56, 67, 127]. This results in a film with a

honeycombed structure, which dissolves quickly giving a fresh mouth sensation. Foamburst™'s patency was granted in September 2004.

7.5 Rapidfilm®

The proprietary Rapidfilm® technology is a cutting-edge, mucoadhesive, fast dissolving oral dosage form and is based on water-soluble polymers and is a patented and commercial technology developed by German based company, Tesa Labtec GmbH [14]. The films typically have a size range of 3-9 cm^2 and a thickness of 50 - 500 μm and the design can vary from single to multi-layer systems. It is a fast disintegrating film which releases the drug rapidly in the mouth and leads to fast systemic absorption of drugs. Rapidfilm® can incorporate a maximum of 30 mg of the API and can either be packaged in boxes or in the RapidCard® which is designed in the format of credit-card. Among the several generic Rx Rapidfilm® products, Ondansetron Rapidfilm® obtained its marketing authorization from the EU in March 2010, as the world's first pharmaceutical product to be approved based on the oral dissolvable film technology. The product is marketed in Europe by Norgine under the tradename Setofilm® and in Canada by Takeda under the tradename Ondisolve® [14].

8 BENEFITS OF FAST-DISSOLVING ORAL THIN FILMS

8.1 Advantages over the conventional dosage forms

Oral thin films disintegrate and dissolve more quickly than the traditional or conventional solid oral dosage forms. These films are very portable and less friable hence the probability of it getting damaged is lower when compared to fast dissolving tablets and capsules [15]. With regard to drug stability, fast dissolving films are more desirable than the corresponding fast disintegrating tablets [11]. The packaging integrity of oral thin films is better than in liquids and other solid dosage forms in terms of environmental impact. Even some of the preservatives used in liquids dosage forms are not suitable for use in paediatrics. Fast dissolving films overcome challenges such as the cumbersomeness of shaking bottles containing liquid formulations to achieve accurate dose titration; thereby avoiding dose errors [54].

8.2 Clinical merits

Fast dissolving films present with a high degree of elegance and are very appealing. These films are appropriate for administration in paediatrics, geriatrics and even the uncooperative such as mental health patients [22]. Oral thin films can also be useful where a rapid onset of action is desired including; coughing, motion sickness, asthma, bronchitis and sudden episodes of allergic attacks. They are easy to administer without choking especially for patients with swallowing difficulties. Oral films can be administered anywhere without using water and once it is administered it becomes difficult to spit out especially for children. Fast dissolving films release the medicament faster and therefore achieve better absorption and have the potential of evading the first pass effect if absorbed through the buccal mucosa [54]. By avoiding the first pass effect, it is possible to reduce the dose of drug which would, in turn, minimise the subsequent side-effects [11]. With the formulation design of oral thin films, there are opportunities for taste-masking of unpalatable drugs to improve overall acceptability and compliance [128].

8.3 Marketing advantage

In term of commercial value, companies in the oral thin film manufacturing industry are presented with opportunities to extend the revenue lifespans of products or drugs nearing patent expiration. The award of exclusive marketing right to the new dosage forms would help in expanding their revenue margins [59].

9 FUTURE PERSPECTIVES

Oral thin films have a wide range of potential future applications not just in the pharmaceutical industry but also the nutraceutical and cosmeceutical industries with a future prospect of generating huge financial benefits through manufacturers ability to extend their products patent life cycles, and therefore will continue to attract interest from all the major stakeholders including patients, clinicians, academic researchers, pharmaceutical industries and regulatory agencies. The use of oral thin films is expected to contribute towards improved compliance and drug therapy outcomes in paediatric and geriatric patients. This will be driven in part by the new regulatory requirements for these vulnerable patient groups to be taken into consideration from the point of drug discovery and development rather than the conventional reformulation and titration

from normal adult dosage forms. Another key driving force will be the increasing number of the geriatric demographic within patient populations worldwide.

10 EXECUTIVE SUMMARY

Oral thin film technology

- This review provided an overview of the need for oral thin films; the material and patient considerations in the design, formulation and characterization of oral thin films.
- It also showcased the benefits of oral thin film technology and the potential it presents, especially in drug delivery in paediatric and geriatric patients.

General attributes

- Oral thin films are more user-friendly than conventional dosage forms, such as tablets, capsules and liquids; due to the many associated challenges including non-compliance, lower bioavailability, and inconvenience in administration.
- Oral thin films are easier to administer and swallow without the need for water, they ensure faster and better drug absorption into the bloodstream.
- Oral thin films combine the advantages of both solid and liquid oral dosage forms. These include being more portable than syrups, capsules and tablets and therefore less expensive in terms of freight costs. Therefore oral thin films are generally more cost-effective than the traditional or conventional dosage forms.

Manufacture of oral thin films

- Oral thin films can integrate most available drugs, although low dose micronized drugs are the most ideal. Water-soluble polymers are used to form the matrix of oral thin films and other components include; plasticizers, surfactants, permeation enhancers, saliva stimulating, colouring, thickening, sweetening and flavouring agents.
- The acceptance oral thin films by patients is essential to its compliance. Practically, most of the excipients used in their formulation have been used in traditional dosage forms such as tablets and are allowed for use in food and neutraceuticals. Good appearance, acceptable taste and palatability as well as a good mouthfeel are essential patient considerations of oral thin films.

Methods of manufacture of fast dissolving oral thin films

- Solvent casting is the widely used method for the manufacture of oral thin films while the HME method is an innovative alternative to formulation of oral thin films, in particular its ability to mask bitter taste of drugs without use of taste masking agents and also avoiding use of organic solvents.

Regulatory requirements of fast dissolving thin films

- Although the EMA and FDA have recently provided guidelines for industry, especially in development of formulations for vulnerable patient groups such as paediatric and geriatric populations, more research is required to establish global standards since most of the reported studies vary greatly in the methodology and approaches and it is difficult to tell which is most appropriate.
- Parameters used in the characterization of oral thin films include; surface pH and swelling index, adequate moisture content and surface morphology, good mechanical properties and acceptable organoleptic indices, uniformity in weight and thickness, as well as *in vitro* disintegration, dissolution and *in vivo* pharmacokinetic profiles are important for meeting the required specifications.

Benefits of fast dissolving oral thin films

- Fast dissolving oral thin films have two key benefits; the first is for the patients which helps improve clinical efficacy and patient compliance, while the second benefit relates to commercial advantage it brings to pharmaceutical industry, through extending of patent life cycles for their drug portfolios.

REFERENCES

1 York P. The design of dosage forms. Part 1 in: Aulton M, Taylor K (Eds). *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. 4th Ed. Elsevier Ltd, London, 7–19 (2013).

2 Rathbone MJ, Senel S, Pather I (Eds). *Oral Mucosal Drug Delivery and Therapy*. Springer US, Boston, MA (2015).

3 Tuleu C, Wright D. 43: Design and administration of medicines for children and the elderly. In: Aulton ME, Taylo KMG (Eds). *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. Elsevier Ltd, London, 751–765 (2013). ** This is a very important contribution in the form of a book chapter, as it brings the concept of designing medicines for paediatric and geriatric patients from academic and industrial research realm into the mainstream teaching of pharmacy and pharmaceutical science students as potential researchers of the future.

4 Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: Benefits and limitations of current platforms. *Expert Opin. Drug Deliv*. 12(11), 1727–1740 (2015).

5 Liu F, Ranmal S, Batchelor HK *et al.* Patient-centred pharmaceutical design to improve acceptability of medicines: Similarities and differences in paediatric and geriatric populations. *Drugs* 74(16), 1871–1889 (2014).

6 Boateng J. Drug delivery innovations to address global health challenges for pediatric and geriatric populations (through improvements in patient compliance). *J. Pharm. Sci.* 106(11), 3188–3198 (2017). * This spells out the importance of using formulation design and redesign as a cheaper means of improving patient compliance in paediatric and geriatric patient groups.

7 Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. *Int. J. Chemtech. Res.* 2(1), 576–583 (2010).

8 Gauri S, Kumar G. Fast dissolving drug delivery and its technologies. *The pharma innovation* 1(2) (2012).

9 Jaiswal H. Oral Strip Technology: A review. *Ind. J. Pharm. Biol. Res.* 2(2), 130 (2014).

10 Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. *Expert Opin. Drug Deliv.* 8(3), 299–316 (2011).

11 Silva BMA, Borges AF, Silva C, Coelho JFJ, Simões S. Mucoadhesive oral films: The potential for unmet needs. *Int. J. Pharm.* 494(1), 537–551 (2015).

12 Sloboda M, Barnhart S. Formulation flexibility broadens the scope for oral thin film technology. *Adhesive Res*, 22–24 (2011).

13 Visser JC, Woerdenbag HJ, Hanff LM, Frijlink HW. Personalized Medicine in Pediatrics: The Clinical Potential of Orodispersible Films. *AAPS Pharm. SciTech*. 18(2), 267–272 (2017).

14 Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. *Int. J. Pharma. Investig*. 3(2), 67-76 (2013).

15 Supriya M, Pallavi K, Munira M. Rapid Dissolve Solid Oral Dossage Form. *LAP*. (2013).

16 Schlatter AF, Deathe AR, Vreeman RC. The Need for Pediatric Formulations to Treat Children with HIV. *AIDS Res. Ther.* 5, 1–8 (2016).

17 Zajicek A, Fossler MJ, Barrett JS *et al.* A Report from the Pediatric Formulations Task Force: Perspectives on the State of Child-Friendly Oral Dosage Forms. *AAPS J.* 15(4), 1072–1081 (2013).

18 Scarpa M, Stegemann S, Hsiao W-K *et al.* Orodispersible films: Towards drug delivery in special populations. *Int. J. Pharm.* 523(1), 327–335 (2017).

19 Vondrak B, Barnhart S. Dissolvable Films for Flexible Product Format. *Pharm. Tech.* 32(4), s20 (2008).

20 Chan R. Oral thin films – Realms of possibility? *ONdrugDelivery Magazine* 69, 12–17 (2016).

21 Auda SH, El-Badry M, Ibrahim MA. Design, Formulation and Characterization of Fast Dissolving Films containing Dextromethorphan. *Digest J. Nanomat. Biostruct.* 9(1), 133–141 (2014).

22 Alipour S, Akbari S, Ahmadi F. Development and in vitro evaluation of fast-dissolving oral films of ondansetron hydrochloride. *Trends Pharm. Sci.* 1(1), 25–30 (2015).

23 Patil PC, Shrivastava SK, Vaidehi S, Ashwini P. Oral fast dissolving drug delivery system: A modern approach for patient compliance. *Int. J. Drug Regul. Aff.* 2(2), 49–60 (2014).

24 Heer D, Aggarwal G, Kumar SL. Recent trends of fast dissolving drug delivery system- an overview of formulation technology. *Pharmacophore* 4(1), 1–9 (2013).

25 Aggarwal J, Singh G, Saini S, Rana AC. Fast dissolving films: A novel approach to oral drug delivery. *Int. Res. J. Pharm.* 2(12), 69–74 (2011).

26 Dharmasthala S, Shabaraya AR, Andrade GS, Shriram RG, Hebbar S, Dubey A. Fast Dissolving Oral Film of Piroxicam: Solubility Enhancement by forming an Inclusion Complex with β-cyclodextrin, Formulation and Evaluation. *J. Young Pharm.* 11(1), 1–6 (2018).

27 Sharma PK, Sharma PK, Darwhekar GN, Shrivastava B. Formulation and evaluation of mouth dissolving film of tadalafil. *J. Drug Deliv. Ther.* 7(7), 52–55 (2017).

28 Gupta M.M PMG, Kedawat M. Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of Meclizine hydrochloride with ÃŸ-cyclodextrin. *J. Appl. Pharm. Sci.* 1(9), 150–153 (2011).

29 Kumar PV, Kumar YS. Development and optimization of quinapril fast dissolving oral films. *Int. J. Pharm. Sci. Drug Res.* 10(4), 329-334 (2018).

30 Maniruzzaman M, Farias S, Slipper IJ *et al.* Development and optimization of ketoconazole oral strips by means of continuous hot-melt extrusion processing. *J. Pharm. Pharmacol.* 68(7), 890–900 (2016).

31 Carpenter G, Maheshwari RK. Formulation and development of fast dissolving oral film of a poorly soluble drug, frusemide with improved drug loading using mixed solvency concept and its evaluation. *J. Drug Deliv. Ther.* 8(6), 132–141 (2018).

32 Hosny KM, El-say KM, Ahmed OA. Optimized sildenafil citrate fast orodissolvable film: A promising formula for overcoming the barriers hindering erectile dysfunction treatment. *Drug Delivery* 23(1), 355–361 (2014).

33 Hassanien ST, Yehia IK. Formulation and evaluation of orodispersible film of sildenafilcitrate. *Int. J. Pharm. Pharm*. Sci. 6, 81–86 (2014).

34 Chaudhary H, Gauri S, Rathee P, Kumar V. Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box–Behnken statistical design. *Bulletin of Faculty of Pharmacy, Cairo University* 51(2), 193–201 (2013).

35 Raghavendra HL, Kumar GP. Development and Evaluation of Polymer-bound Glibenclamide Oral Thin Film. *J. Bioequiv. Availab.* 9(1), 324 - 330 (2016).

36 Teja D, Jasvanth E, Mounika B, Nalluri BN. Formulation and Evaluation of Chlorpheniramine Maleate Mouth Dissolving Films. *J. Drug Delivery Ther.* 9(1-s), 244–251 (2019).

37 Mahmood SZ, Sabry HS, Yousif NZ, Salman ZD. Optimization and evaluation of Chlorpheniramine Maleate oral strip for paediatric use. *Asian J. Pharm. Clin. Res.* 11(12), 548 (2018).

38 Mishra R, Amin A. Formulation development of taste-masked rapidly dissolving films of cetirizine hydrochloride. *Pharm. Technol.* 33(2), 48–56 (2009).

39 Mishra R, Amin A. Optimization and characterization of rapidly dissolving films of cetirizine hydrochloride using cyclodextrins for taste masking. *Int. J. Pharm. Tech. Res.* 5, 536–552 (2013).

40 Rao PS, Reddy TRM. Development and Evaluation of Mouth Dissolving Films Containing Selegiline. *Int. J. Pharm. Sci. Drug Res.* 10(4), 315–321 (2018).

41 Murata Y, Kofuji K, Maida C. Control of Drug Dissolution Rate from Film Dosage Forms Containing Valsartan. Int. Sch. Res. Notices. 2016, 1–5 (2016).

42 Linku A, Sijimol J. Formulation and Evaluation of Fast Dissolving Oral Film of Anti-Allergic Drug. *Asian J. Pharm. Res. Dev.* 6(3), 5–16 (2018).

43 Nishigaki M, Kawahara K, Nawa M, *et al.* Development of fast dissolving oral film containing dexamethasone as an antiemetic medication: Clinical usefulness. *Int. J. Pharm.* 424(1-2), 12–17 (2012).

44 Shimoda H, Taniguchi K, Nishimura M *et al.* Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. *Eur. J. Pharm. Biopharm.* 73(3), 361–365 (2009).

45 Senta-Loys Z, Bourgeois S, Pailler-Mattei C, Agusti G, Briançon S, Fessi H. Formulation of orodispersible films for paediatric therapy: Investigation of feasibility and stability for tetrabenazine as drug model. *J. pharm. Pharmacol.* 69(5), 582–592 (2017).

46 Sharma A, Sriganesan P. Formulation development and optimization of fast dissolving film containing carvedilol nanocrystals for improved bioavailability. *J. Drug Deliv. Ther.* 8(6), 74–81 (2018).

47 Murata Y, Kofuji K, Nishida N, Kamaguchi R. Development of Film Dosage Form Containing Allopurinol for Prevention and Treatment of Oral Mucositis. *ISRN Pharmaceutics* 2012, 1–5 (2012).

48 Khan S, Boateng JS, Mitchell J, Trivedi V. Formulation, Characterisation and Stabilisation of Buccal Films for Paediatric Drug Delivery of Omeprazole. *AAPS PharmSciTech* 16(4), 800–810 (2015). *This addresses a cheap and effective way of addressing one of the problems of drug formulation processing and storage of drugs commonly prescribed to the paediatric population.

49 Khan S, Trivedi V, Boateng J. Functional physico-chemical, ex vivo permeation and cell viability characterization of omeprazole loaded buccal films for paediatric drug delivery. *Int. J. Pharm.* 500(1-2), 217–226 (2016). * This addresses the importance of ensuring that formulations developed for paediatric patients satisfy the critical performance characteristics including safety, which is of vital importance

50 Bala R, Khanna S, Pawar P. Design optimization and in vitro-in vivo evaluation of orally dissolving strips of clobazam. *J. Drug Deliv*. 2014, 392783 (2014).

51 Kumria R, Nair A, Wadhwa J, Bansal S, Gupta V. Oral buccoadhesive films of ondansetron: Development and evaluation. *Int. J. Pharma. Investig.* 3(2), 112 (2013).

52 Karthikeyan D, Sri S, Kumar CS. Development of Fast Dissolving Oral Film Containing of Rizatriptan Benzoate as an Anti-Migraine Medication. *Indo American J. Pharm. Res.* 3(3), 2642–2654 (2013).

53 Vijaya Sri K, Rohini P, Kamalakar Reddy G. Montelukast sodium oral thin films: Formulation and invitro evaluation. *Asian J. Pharm. Clin. Res.* 5, 266–270 (2012).

54 Dixit RP, Puthli SP. Oral strip technology: Overview and future potential. *J. Control. Rel.* 139(2), 94–107 (2009).

55 Prajapati ST, Patel CG, Patel CN. Formulation and Evaluation of Transdermal Patch of Repaglinide. *ISRN Pharmaceutics* 2011(1), 1–9 (2011).

56 Bala R, Khanna S, Pawar P, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. *Int. J. Pharm. Investig.* 3(2), 67 (2013).

57 Pathare YS, Hastak VS, Bajaj AN. Polymers used for fast disintegrating oral films: A review. *Int. J. Pharm. Sci. Rev. Res.* 21(1), 169-178 (2013).

58 Rathbone MJ, Pather I, Şenel S. Overview of Oral Mucosal Delivery. In: Rathbone MJ, Senel S, Pather I (Eds). *Oral Mucosal Drug Delivery and Therapy*. Springer US, Boston, MA, 17–29 (2015).

59 Karki S, Kim H, Na S-J, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. *Asian J. Pharm. Sci.* 11(5), 559–574 (2016).

60 Shanmugam S. Oral Films: A Look Back. *Clin. Pharmacol. Biopharm*. 5(2), 2–4 (2016).

61 Amin PM, Gangurde AB, Alai PV. Oral film technology: Challenges and future scope for pharmaceutical industry. *Int. J. Pharm. Pharm. Res.* 3, 183–203 (2015).

62 Vuddanda PR, Montenegro-Nicolini M, Morales JO, Velaga S. Effect of plasticizers on the physico-mechanical properties of pullulan based pharmaceutical oral films. *Eur. J. Pharm. Sci.* 96, 290–298 (2017).

63 Crowley MM, Zhang F, Repka MA *et al.* Pharmaceutical Applications of Hot-Melt Extrusion: Part I. *Drug Dev. Ind. Pharm.* 33(9), 909–926 (2007).

64 Radhakishan UR, Chavan V, Tribhuvan N. Mouth dissolving films and their patents: An overview. *Int. Res. J. Pharm* 3(9), 39–42 (2012).

65 Sekhon BS. Surfactants: Pharmaceutical and Medicinal Aspects. *J. Pharm. Technol. Res. Manag.* 1(1), 43–68 (2013).

66 Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharm. J.* 24(5), 537–546 (2016).

67 Khatoon N, Rao NR, Reddy BM. Overview on fast dissolving oral films. *Int. J. Chem. Pharm. Sci.* 1(1), 63–75 (2013).

68 Bilal M, Mahboob H, Riaz T, Jamshaid M, Bashir I, Zulfiqar S. Oral Films: A Comprehensive Review. *Int. Curr. Pharm. J.* 5(12), 111–117 (2016).

69 Sohi H, Sultana Y, Khar RK. Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches. *Drug Dev.Ind. Pharm.* 30(5), 429–448 (2004).

70 Behrens M, Meyerhof W. Signalling in the Chemosensory Systems. *Cell. Mol. Life Sci.* 63(13), 1501–1509 (2006).

71 Meyerhof W, Batram C, Kuhn C *et al.* The Molecular Receptive Ranges of Human TAS2R Bitter Taste Receptors. *Chemical Senses* 35(2), 157–170 (2010).

72 Shet N, Vaidya I. Taste masking: A pathfinder for bitter drugs. *Int. J. Pharm. Sci. Rev. Res* 18(2), 1–12 (2013).

73 Nunn T, Williams J. Formulation of medicines for children. *Br. J. Clin. Pharmacol.* 59(6), 674–676 (2005).

74 Boateng J, Okeke O. Evaluation of Clay-Functionalized Wafers and Films for Nicotine Replacement Therapy via Buccal Mucosa. *Pharmaceutics* 11(3) (2019).

75 Vikas S, Seema S, Gurpreet S, C RA, Baibhav J. Penetration Enhancers: A novel strategy for enhancing transdermal drug delivery: review. *Int. Res. J. Pharm.* 2(12), 32–36 (2011).

76 Dodla S, Velmurugan S. Buccal penetration enhancers: An overview. *Asian J. Pharm. Clin. Res.* 6(3), 39–47 (2013).

77 Singla V, Saini S, Singh G, Rana AC, Joshi B. Penetration enhancers: A novel strategy for enhancing transdermal drug delivery. *Int. Res. J. Pharm.* 2(12), 32–36 (2011).

78 Woertz C, Kleinebudde P. Development of orodispersible polymer films containing poorly water soluble active pharmaceutical ingredients with focus on different drug loadings and storage stability. *Int. J. Pharm.* 493(1-2), 134–145 (2015).

79 Leung S-H, Leone R, Kumar L, Kulkarni N, Sorg A. Fast dissolving orally consumable films. Google Patents (2003).

80 Cram A, Breitkreutz J, Desset-Brèthes S, Nunn T, Tuleu C. Challenges of developing palatable oral paediatric formulations. *Int. J. Pharm.* 365(1-2), 1–3 (2009).

81 Krampe R, Visser JC, Frijlink HW, Breitkreutz J, Woerdenbag HJ, Preis M. Oromucosal film preparations: Points to consider for patient centricity and manufacturing processes. *Expert Opin. Drug Deliv.* 13(4), 493–506 (2016).

82 Preis M, Knop K, Breitkreutz J. Mechanical strength test for orodispersible and buccal films. *Int. J. Pharm.* 461(1-2), 22–29 (2014).

83 van Riet-Nales DA, Schobben AFAM, Vromans H, Egberts TCG, Rademaker CMA. Safe and effective pharmacotherapy in infants and preschool children: Importance of formulation aspects. *Arch. Dis. Child.* 101(7), 662–669 (2016).

84 European Medicines Agency. *Guideline on Pharmaceutical Development of Medicines for Paediatric Use.* Committee for Medicinal Products for Human Use, EMA/CHMP/QWP/805880/2012 Rev. 2,

(2013).85 Preis M, Breitkreutz J, Sandler N. Perspective: Concepts of printing technologies for oral film formulations. *Int. J. Pharm.* 494(2), 578–584 (2015).

86 Preis MK. Oromucosal Film Preparations for Pharmaceutical Use-Formulation Development and Analytical Characterization, Universitäts-und Landesbibliothek der Heinrich-Heine-Universität Düsseldorf. (2014)

87 Tripathi A, Parmar D, Patel U, Patel G, Daslaniya D, Bhimani B. Taste masking: A novel approach for bitter and obnoxious drugs. *J. Pharm. Sci. Biosci. Res.* 1(3), 36–142 (2011).

88 Cilurzo F, Cupone IE, Minghetti P, Buratti S, Gennari CGM, Montanari L. Diclofenac fast-dissolving film: Suppression of bitterness by a taste-sensing system. *Drug Dev. Ind. Pharm.* 37(3), 252–259 (2010).

89 ElMeshad AN, El Hagrasy AS. Characterization and Optimization of Orodispersible Mosapride Film Formulations. *AAPS Pharm. Sci. Tech*. 12(4), 1384–1392 (2011).

90 Visser JC. *Orodispersible films as pharmacy preparations: Let's Get Flexible*. PhD Thesis, University of Groningen, Groningen (2017)

91 Bonsu MA, Ofori-Kwakye K, Kipo SL, Boakye-Gyasi ME, Fosu MA. Development of Oral Dissolvable Films of Diclofenac Sodium for Osteoarthritis Using Albizia and Khaya Gums as Hydrophilic Film Formers. *J. Drug Deliv*. 2016, 1-11 (2016).

92 Mahajan A, Chhabra N, Aggarwal G. Formulation and characterization of fast dissolving buccal films: A review. *Sch. Res. Library, Der Pharmacia Lettre* 3(1), 152–165 (2011).

93 Buanz ABM, Belaunde CC, Soutari N, Tuleu C, Gul MO, Gaisford S. Ink-jet printing versus solvent casting to prepare oral films: Effect on mechanical properties and physical stability. *Int. J.Pharm.* 494(2), 611–618 (2015).

94 Kulkarni CS. Novel formulations of a poorly soluble drug using the extrusion process, University of Bradford, UK. PhD Thesis (2015).

95 Joshua JM, Hari R, Jyothish FK, Surendran SA. Fast Dissolving Oral Thin Films: An Effective Dosage Form for Quick Releases. *Drugs* 11, 12 (2016).

96 Maniruzzaman M, Douroumis D, Boateng SJ, Snowden JM. Hot-Melt Extrusion (HME): From Process to Pharmaceutical Applications. In: Sezer AD (Ed.). *Recent Advances in Novel Drug Carrier Systems*. InTech (2012).

97 Yellanki SK, Jagtap S, Masareddy R. Dissofilm: A Novel Approach for Delivery of Phenobarbital; Design and Characterization. *J. Young Pharm.* 3(3), 181–188 (2011).

98 Maniruzzaman M, Boateng JS, Chowdhry BZ, Snowden MJ, Douroumis D. A review on the taste masking of bitter APIs: Hot-melt extrusion (HME) evaluation. *Drug Dev. Ind. Pharm.* 40(2), 145–156 (2013).

99 Maniruzzaman M, Boateng JS, Bonnefille M, Aranyos A, Mitchell JC, Douroumis D. Taste masking of paracetamol by hot-melt extrusion: An *in vitro* and *in vivo* evaluation. *Eur. J. Pharm. Biopharm.* 80(2), 433–442 (2012). ** This article highlights the importance of confirming predictive in vitro models used to test for taste masking of bitter drugs, using in vivo human panels to reduce the chances of failure when administered to patients, especially paediatrics, where taste is one of the major barriers to compliance.

100 Pimparade M, Vo A, Maurya SA, *et al.* Development and Evaluation of an Oral Fast Disintegrating Anti-Allergic Film Using Hot-melt Extrusion Technology. *Eur. J. Pharm. Biopharm.* 119, 81-90 (2017).

101 Repka MA, Battu SK, Upadhye SB *et al.* Pharmaceutical Applications of Hot-Melt Extrusion: Part II. *Drug Dev. Ind. Pharm.* 33(10), 1043–1057 (2008).

102 Ridhurkar D, Vajdai A, Zsigmond Z. Hot-melt extrusion (HME) and its application for pharmacokinetic improvement of poorly water-soluble drugs. *PTB Reports,* 2(3), 47–51 (2016).

103 Garsuch V, Breitkreutz J. Novel analytical methods for the characterization of oral wafers. *Eur. J. Pharm. Biopharm.* 73(1), 195–201 (2009).

104 Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. *Eur. J. Pharm. Biopharm.* 77(2), 187–199 (2011).

105 Khurana S, Madhav NS, Tangri P. Mucoadhesive drug delivery: Mechanism and methods of evaluation. *Int. J. Pharm. Biosci.* 2(1), 458–467 (2011).

106 Kianfar F, Antonijevic MD, Chowdhry BZ, Boateng JS. Formulation Development of a Carrageenan Based Delivery System for Buccal Drug Delivery Using Ibuprofen as a Model Drug. *J. Biomater. Nanobiotechnol.* 2(5), 582–595 (2011).

107 Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: Swelling, mechanical, and bioadhesive properties. *J. Pharm. Pharm. Sci.* 2(2), 53–61 (1999).

108 Kumria R, Nair AB, Goomber G, Gupta S. Buccal films of prednisolone with enhanced bioavailability. *Drug Deliv.* 23(2), 471–478 (2016).

109 Boateng JS, Ayensu I. Preparation and characterization of laminated thiolated chitosan-based freeze-dried wafers for potential buccal delivery of macromolecules. *Drug Del Ind Pharm*. 40(5), 611-618 (2014). .

110 Baranowski P, Karolewicz B, Gajda M, Pluta J. Ophthalmic Drug Dosage Forms: Characterisation and Research Methods. *The Scientific World Journal* 2014(7), 1–14 (2014).

111 Panomsuk S. A study of the hydrophilic cellulose matrix: Effect of indomethacin and a water-soluble additive on swelling properties. *Int. J. Pharm.* 126(1-2), 147–153 (1995).

112 Dandagi PM, Rath SP, Gadad AP, Mastiholimath VS. Taste Masked Quinine Sulphate Loaded Solid Lipid Nanoparticles for Flexible Pediatric Dosing. *Ind. J. Pharm. Edu. Res*. 48(suppl), 93–99 (2014).

113 Mazumder S, Pavurala N, Manda P, Xu X, Cruz CN, Krishnaiah YSR. Quality by Design approach for studying the impact of formulation and process variables on product quality of oral disintegrating films. *Int. J. Pharm.* 527(1-2), 151–160 (2017).

114 Choudhary DR, Patel VA, Chhalotiya UK, Patel HV, Kundawala AJ. Formulation and Evaluation of Fast Dissolving Film of Levocetirizine Dihydrochloride Using Different Grades of Methocel. *J. Pharm. Res.* 4(9), 2919–2924 (2011).

115 Gorle AP, Gattani SG. Design and Evaluation of Polymeric Ocular Drug Delivery System. *Chem. Pharm. Bull.* 57(9), 914–919 (2009).

116 Julia H, Martin K, Roland B. Individual dosing and controlled drug delivery with matrix-minitablets for paediatric use. *The 3rd Annual Conference of the European Paediatric Formulation Initiative in* Berlin, Germany (2010).

117 Hoang Thi TH, Morel S, Ayouni F, Flament M-P. Development and evaluation of taste-masked drug for paediatric medicines – Application to acetaminophen. *Int. J. Pharm.* 434(1-2), 235–242 (2012).

118 Ortega-Toro R, Jiménez A, Talens P, Chiralt A. Properties of starch–hydroxypropyl methylcellulose-based films obtained by compression molding. *Carbohydrate Polymers* 109, 155–165 (2014).

119 Sultana F, Arafat M, Pathan SI. Preparation and evaluation of fast dissolving oral thin film of caffeine. *Int. J. Pharm Bio. Sci.* 3(1), 153–161 (2013).

120 Keshari A, Sharma PK, Nayyar P. Fast dissolving oral film: A novel and innovative drug delivery system. *Int. J. Pharm. Sci. Res.* 5(3), 92–95 (2014).

121 Kayumba P. Taste-masked quinine formulations for flexible pediatric drug dosing in oral treatment of malaria, PhD Thesis. Ghent University. (2007)

122 Mennella JA, Spector AC, Reed DR, Coldwell SE. The Bad Taste of Medicines: Overview of Basic Research on Bitter Taste. *Clin. Ther.* 35(8), 1225–1246 (2013).

123 Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: Identifying the needs and recognizing the challenges. *J. Pharm. Pharmacol.* 59(8), 1043–1055 (2007).

124 Jain H, Panchal R, Pradhan P, Patel H, Pasha TY. Electronic tongue: A new taste sensor. *Int. J. Pharm. Sci. Rev. Res.* 5(2), 91–96 (2010).

125 Jyothi AA, Mounika P, Vineesha S, Mehdia S, Dutt AN. Formulation Development and Evaluation of Oral Thin Films-Diphenhydramine HCl. *Int. J. Pharm. Sci. Res.* 4(9), 3484–3488 (2013).

126 Dnyaneshwar HR, Wale KK, Sayyed SF, Chaudhari SR. A Review: Oro-dispersible Film Dosage Form. *World J. Pharm. Res.* 3(5), 1093–1111 (2014).

127 Siddiqui MN, Garg G, Sharma PK. A short review on-a novel approach in oral fast dissolving drug delivery system and their patents. *Adv. Biol. Res.* 5(6), 291–303 (2011).

128 Douroumis D. *Hot-Melt Extrusion: Pharmaceutical Applications*. John Wiley & Sons, Ltd, Chichester, UK (2012).

129 Patil H, Tiwari RV, Repka MA. Hot-Melt Extrusion: from theory to application in pharmaceutical formulation, *AAPS PharmSciTech*. 17(1): 20–42 (2016).

130 Hanning SM, Lopez FL, Wong IC, Ernest TB, Tuleu C, Orlu Gul M. Patient centric formulations for paediatrics and geriatrics: Similarities and differences. *Int J Pharm*. 512(2), 355-359 (2016). ** This is a timely contribution that identifies the similarities and differences between paediatric patients and how these should be exploited in the optimum design and development of safe and effective dosage forms for each group in a more or less 'personalised' way.