Oral films: current status and future perspectives

II – Intellectual property, technologies and market needs

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1 Introduction

The oral route remains the most preferred for the general population [1]. It is easier, non-invasive, convenient and flexible, and generally oral formulations have a lower cost of production for the pharmaceutical companies. These facts justify why the oral delivery market holds 52% of the market share remaining the largest sector in the overall drug delivery market [2-4]. Although the majority of drugs are administered in the form of tablets and capsules, several groups of patients have serious swallowing difficulties. It is estimated that almost 28% of the general population have frequent problems in swallowing medicines that is often the cause of poor patient compliance [5]. This is commonly associated to dangerous tablets and capsules' modifications, such as splitting or crushing, related with dosage inaccuracy and drug therapy inefficiency or overdosing [6]. In order to overcome these issues, fast dissolving delivery systems are gaining considerable attention. Among them, oral films have emerged and have been dragged by this urgent market need.

There is no strong evidence or consensus about the date for the first reference of orodispersible delivery systems [7] but the most likely pioneer in the conception of orodispersible films was Deadman Frederic in 1960s [8]. Nevertheless, it remained just a concept until 2001 when Pfizer introduced in the market the major orodispersible film blockbuster, the Listerine® Pocket Packs® [9].

There is an evident trend that the pharmaceutical field is moving from the conventional and traditional to the innovative and patient-centered developments. There is also an increase demand of the authorities for knowledge, in order to improve the quality of the products, and the optimization and lean of the resources.

This section of the review highlights the Intellectual Property developed in this field, looking over the major players in the area, their platform technologies and all the commercial evolution through a summary market outlook and trends.

2 Intellectual Property

The drug delivery technology is an area with extensive intellectual property protection which is extremely important and required considering the high competitiveness of this fast-evolving field. There are a considerable number of institutions developing oral films, which can be easily confirmed by the constant growing number of patent applications. In fact, the increasing number of patents filled each year is impressive and more than 132 patent families have been identified and at least 30 companies / institutions are developing these technological platforms [10]. Until 2011, the majority of the patents were filled in the US and Japan, by the top players such as MonoSol and Kyukyu Pharmaceuticals Co.,LTD, with Europe gaining some ground in the recent years with LTS Lohman Therapy-Systems (LTS), Labtec Pharma, Hexal Pharmaceuticals and others. Additionally, LTS and MonoSol are clearly the major players with a broader technology coverage concerning the intellectual property, highlighting the diversified and fuelled research of these companies in the field [10]. At the moment according to the recent published Root Analysis report,

MonoSol is the most prominent player in the oral thin films, with nine products already on the market based on its own technology [11].

Regarding intellectual property protection, an exhaustive search in free patent databases (google patents, Espacenet, WIPO) reveals that the composition patents are the larger slice in the overall patents filled. Among them, few are restricted to a specific therapy or drug substance, and the majority is therapeutically broader and focused in the composition of the technology, claiming essentially the film forming polymer(s), crucial for the matrix formation. The process patents have also some relevance, but only a few are restricted to a specific drug, therapy or method of use.

The most patented polymers are polysaccharides, including starch, cellulose and its derivatives (Figure 6). As already described in the part 1 of this review, these are two large groups of polymers that can be subdivided into subclasses according to the modifications and substituents added to the native natural polymer backbones.

Figure 6 – Overall Scenario of polymers usage. The Polysaccharide group comprises starch derivatives, pectin, gums, dextrans and alginates; other polymers group includes polyvinyl and polyethylenoglycol polymers and co-polymers; the proteins groups consists of soy proteins, casein, zein, collagen and others; the acrylates groups refers mainly to methacrylate and polyacrylic polymers.

The use of the majority of hydrophilic polymers in formulations of oral films is already protected by several patents, restricting the possibility of developing formulations that do not infringe existing patents and capable of being protected by new ones. During the last years the development of new polymers suitable to this technological platform was scarce, leading to an increasing number of process patent applications, and patent formulations related with specific drug substances or therapies.

Furthermore, the difficulty in innovating in the formulation composition due to the small number of suitable excipients had probably contributed to new directions in this research field, such as the development of new manufacturing processes [12, 13] (see part 1 review), or the usage of oral films as drug delivery systems for biotechnology products (e.g. vaccines and insulin) [14-17].

3 Technological platforms

The majority of the top player companies referred above followed a similar pattern. Generally, a new and innovative technological platform is developed (like an oral film placebo) and then several drug candidates are evaluated and considered to be incorporated in the film. Obviously,

this strategy implies necessarily the development of a versatile oral film platform, which in turn may suffer some modifications depending on the drug substance characteristics and the desired final dosage form performance.

Furthermore, it is common in this market segment the establishment of partnerships between oral film developers / manufacturers and other pharmaceutical companies researching new chemical entities, developing novel uses for existing drugs (repurposing) or companies looking for innovative formulations for their drugs (life-cycle management). This strategy is beneficial to share fixed expenses associated with the product licensing and marketing [18]. Therefore, two different major players may be distinguished in this field: the oral film platform developers, usually the technology owners, and the marketing partners.

Several oral film platforms have been already developed, the majority is listed on Table 4 and some are revised herein.

3.1 Pharmfilm®

MonoSol, one of the pioneer companies in the oral film industry owns a protected drug delivery technology, PharmFilm®. MonoSol's film technology is supposed to be more stable and robust than other conventional dosage forms with a loading capacity up to 80 mg. The Pharmfilm® is a polymeric matrix based on polyethylene oxide and hydroxypropylmethyl cellulose, which normally is related with fast dissolution rates and rapid drug absorption [19]. However, MonoSol claims that this technological platform can be used for both fast dissolving system or buccal delivery. In fact, ondansetron hydrochloride had been successfully incorporated into the PharmFilm® technology as fast-dissolving system and others drug substances such as montelukast sodium, rizatriptan, escitalopram oxalate, donepezil hydrochloride and epinephrine are being considered or under development as oral quick release formulations [20-25]. Additionally, as previously referred, the Pharmfilm® technology is also available as a slower release sublingual formulation (Suboxone® sublingual film) [25].

Moreover, MonoSol has established strategic partnerships to develop biotechnology sublingual and buccal films based on PharmaFilm® technology, such as anti-diabetic oral films or films to deliver a vaccine for universal flu. Together with Midatech, MonoSol has developed Nanoinsulin (insulin gold nanoparticles, MidaForm insulin) to incorporate in the MonoSol's PharmaFilm® buccal film technology, for the potential treatment of diabetes. In the beginning of 2013, this investigational medicinal product was listed as being in clinical development. Nevertheless, another buccal PharmaFilm® loaded with MidaForm nanoparticles, containing insulin and GLP-1, is also in preclinical development [14, 25, 26].

MonoSol in association with BiondVax Pharmaceuticals is developing a sublingual film formulation for vaccination, with the Multimeric-001 (M-001), for the potential prevention of universal influenza infection. It is expected that this type of formulation will allow the stability of the vaccine at room temperature [15, 27].

3.2 RapidFilm®

RapidFilm® is another patented technology developed by Labtec GmbH. The Rapidfilm® is a fast dissolving thin film based on water soluble polymers, non-mucoadhesive, which can vary from single to multilayer design system. This oral film platform is based in a PVA-Starch mixture plasticized with a medium Mw PEG. The composition used allows its fast dissolution rate when in contact with the oral mucosa [28]. It is claimed that RapidFilm® can accommodate up to 30 mg of the drug substances [20] [29]. The ondansetron Rapidfilm® was the first Rx oral film approval

worldwide, but at the moment, there are at least three more Rapidfilm® products in the European market [30] (see table 4).

3.3 VersaFilm™

VersaFilm™ technology was developed and patented by IntelGenx Technologies Corp. Initially developed as an edible film for the instant delivery of savoury flavours to food substrates, VersaFilm™ is now used as a system of choice for indications requiring an immediate onset of action. Thus, the company advances that VersaFilm™'s disintegration time may be wrought from 30 seconds to 10 minutes, and it can be sublingual, depending on the intended application. The maximum drug load claimed is around 40mg. According to IntelGenx pipeline there are several drug substances in consideration or being incorporated in the VersaFilm™ technology. However, only one has recently received a complete response letter from FDA, the rizatriptan VersaFilm™, an oral quick release film for migraine, developed together with RedHill Biopharma Ltd [31, 32].

3.4 Orally and Adhesive Disintegrating Films

KyuKyu Pharmaceuticals Co., Ltd is a Japanese company that also has its own oral film platform technology. Actually, KyuKyu have 2 different technologies the "Orally Disintegrating Film", which dissolves in 10 to 30 seconds and the "Adhesive and Disintegrating Film" that adheres to the oral mucosa and the disintegration time can vary between 30 minutes and 8 hours [33]. KyuKyu presents a large pipeline with several oral dispersible films in the market, mainly in the Asian market. Recently, it started to develop buccal films for the treatment of cancer-related pain and nicotine dependence. In collaboration with Nippon Kayaku, a buccal formulation of fentanyl is being developed and a phase II trial is being conducted [34]. Regarding to the nicotine mucoadhesive disintegrating film, it was in the fourth quarter of 2013 listed as being in lead optimization.

3.5 SmartFilm®

Seoul Pharma has developed the SmartFilm® technology, an oral film with a high loading dose capacity, over 140 mg, capable of incorporating both hydrophilic and hydrophobic drugs, with unique taste masking technology and an eco-friendly manufacturing process (aqueous solution based). This South Korean pharmaceutical company launched Vultis® in the Korea market in 2012, a 140.45mg film formulation of sildenafil citrate. At the end of the same year, Seoul Pharma licensed it out to Pfizer which rebranded it as Viagra [35, 36]. The Sildenafil SmartFilm® technology is a fast dissolving film composition that uses a combination of magnesium oxide and sodium hydroxide to mask the bitter taste of the drug substance. Seoul Pharma is currently seeking and researching other molecules to incorporate in its own oral film technology [37, 38].

3.6 BEMA®

BioDelivery Sciences International owns the worldwide rights of BEMA®, bio-erodible muco-adhesive, drug delivery technology. This drug delivery technology consists in a bioerodible polymer film which adheres quickly to the oral mucosa (less than 5 seconds) with a backing layer that assures the unidirectional diffusion of the drug substance. This multilayer buccal film technology can rapidly deliver a dose of drug across the oral mucosa and is completely dissolved within 15 to 30 minutes. The BEMA® technology may be developed to incorporate several drug substances, especially if a quick onset of action is required, the oral administration dose is not optimal (low oral bioavailability) or if parental administration is not an option [39]. Onsolis®, fentanyl buccal film, was the first product developed and marketed based on BEMA®'s technology, for the management of cancer pain in opioid-tolerant adults. It was launched in 2009 [40], but by March

2012, the Onsolis® production had been temporarily closed in the US, due to FDA concerns regarding the manufacturing process [41]. In January 2014, it was announced that the re-launch of the product is planned to occur in the second half of 2014 [42, 43]. In Europe, the product was approved in October 2010 as Breakyl® [44]. Currently the BEMA® technology is being applied to improve the delivery of other therapies, as the opioid dependence with Bunavail™, previously referred. The base formulation of the BEMA® layers is very similar. Both the active and the backing layer are composed by hydroxypropyl cellulose, hydroxyethyl cellulose, but the active layer presents additional mucoadhesive polymers, as polycarbophil and carboxymethylcellulose sodium. Interestingly the sweetener and flavor are only present in the backing layer [19, 45].

3.7 Bio-FX® Fast-Onset Oral-Cavity ODF

Another technology platform is the Bio-FX® Fast-Onset Oral-Cavity ODF from NAL Pharmaceuticals Ltd. Briefly, it is an oral film formulated with a Bio-FX® absorption enhancer system, which increases the absorption of the drug substances through the oral mucosa with the aim to improve the oral bioavailability of drugs by avoiding the first-pass metabolism and gastrointestinal degradation. This technology also incorporates a especial designed taste-masking system to improve taste and mouthfeel [46]. Currently, there are no available products on the market with this technology, but several are under development.

3.8 Quicksol®

Quicksol® technology is the oral film platform from SK Chemicals that can accommodate a wide variety of drug substances. According to the company's pipeline, several drug substances were loaded, but only two are already on the market, Montfree (Montelukast) ODF and Mvix-S (Mirodenafil) ODF [47]. Mvix-S is a thin, light and portable 50 mg oral film, available since January 2012, with a mirodenafil rate absorption 16.7% higher than Mvix tablet. Additionally, 15 days after its launch, Mvix-S sold over 1 billion units [48].

3.9 Fast-onset sublingual bilayer film

Cynapsus developed a fast-onset sublingual bilayer film of apomorphine, the APL-130277. The apomorphine in its neutral form (which may permit its fast mucosal absorption) is easily oxidized making difficult its incorporation in a film. Therefore, the apomorphine non-neutral form is loaded in one film layer, and a neutralizing agent is incorporated in other film layer, physically separated from each other. The neutralizing agent's layer dissolves quickly upon contact with saliva, allowing a fast reaction with the drug substance for a rapidly absorption. Clinical trials demonstrated that the maximum blood levels were reached within 20 minutes of administration, in the majority of subjects, and that it has a good local tolerability (no irritation). The submission of a FDA 505(b)(2) NDA is expected to 2016, since Cynapsus estimate to complete efficacy and safety studies by the end of 2014 and 2015, respectively. This sublingual formulation had already proved to work in the most severe cases of Parkinson's disease. Moreover, it may also present patient benefits and competitive advantages over the subcutaneous injection available and the inhaled and pulmonary approaches that are still in early development stages. According to their patent application the main polymer may be a cellulose, as HEC and / or a modified starch as maltodextrins, or even a mixture thereof [49].

3.10 Biodegradable transmucosal film

In the first quarter of 2005, Auxilium Pharmaceuticals had licensed an oral drug delivery system, based on the PharmaForm technology after their drug delivery platform acquisition. This platform is a biodegradable transmucosal film that adheres to the upper gum, preferentially above the back

molar, and after that it completely dissolves. PharmaForm technology may allow a more effective delivery of the substances through a higher rate of drug absorption, contributing to achieve the same therapeutic levels with lower doses when compared with the conventional dosage form, shorter onset of action, reduction of first pass metabolism and probably less frequent dosing. Auxilium was using this technology platform to incorporate drug substances for the treatment of overactive bladder, management of pain and androgen replacement therapy. According to the company information, the overactive bladder transmucosal film candidate was supposed to be moving to phase II studies, after being demonstrated that oxybutynin could be administered using the transmucosal film, but no development has been recently reported. Similarly, Fentanyl Pharmaform film, which was in phase I development in 2011, has no recent updated information. Regarding to testosterone transmucosal film (TestoFilm), it was in a phase III trial in the beginning of 2006. However, in the last quarter of the same year Auxilium discontinued the development claiming that the formulation would not be commercially viable [50, 51].

3.11 Eluting Bandage Platform

Pharmedica has an innovative and patented oral film platform, the Eluting Bandage Platform. This is a multiple characteristic platform that can be used as single or multiple layer, with fast or slow disintegration time and for combined or protective treatment. Eluting Bandage Platform is a multi-purpose and multi-functional device that can be used for a large range of products, from fresh breathers to prescription products. Pharmedica was developing oral formulations of insulin for the potential treatment of diabetes which had a launch predicted date for 2013. However, no more information is available, but according to the company's website the insulin, together with cannabinoids, is still listed as a potential product for the Eluting Bandage platform [52].

3.12 Xgel™

Xgel™ film's technology is the basis of Meldex International intellectual property, used in all its film systems: Soluleaves™, Foamburst™ and Wafertab™. Soluleaves™ platform can be designed for fast dissolving release or to adhere to the oral mucosa for a slow release of the drug substance. The Foamburst™ is a variant of the previous technology where an inert gas is passed during the film's manufacture resulting in a honeycomb structure that controls the dissolution rate of the drug substance contributing to a novel mouth sensation. In turn, the Wafertab™ platform is prepared from a placebo Xgel™ film in which the drug substance is added afterwards, thus preventing its exposure to unnecessary heat and moisture. This technology allows the manufacture of unstable drugs and the preparation of multilayer films [20, 53]. In 2007, Meldex was developing nicotine Soluleaves™, but no recent development has been reported. According to the patent information this is a cellulose derivative based film [54].

3.13 Thinsol™

BioEnvelop (or Paladin Labs) has also its own patented technology, the Thinsol™, an oral film based on enzymatically digested carboxy methyl cellulose. This platform is a fast dissolving film (from five to 30 seconds) that allows a drug loading up to 60% and can be used to incorporate heat sensitive drugs, since it can be dried at low temperatures [20, 55-57].

Interestingly, the NeuroHealing Pharmaceuticals Inc. developed an intra-oral slow dissolving mucoadhesive thin film based on the original formulation of Listerine Pocket Packs®. This modified oral film was developed to incorporate 1mg of tropicamide for sialorrhea treatment. In fact, this buccal film platform, designated by the code name NH004, has two main modifications: additional mucoadhesive properties and a slower dissolution capability. Therefore the NH004 easily adheres to the oral mucosa to dissolve slowly, over a period of 60-90 minutes, so the drug can be absorbed

locally near the submandibular salivary gland [58]. Currently a phase II clinical trial is being conducted in order to evaluate the safety and efficacy of tropicamide thin films in hypersalivation Parkinson's patients treatment [59].

3.14 Schmelzfilmen

The “Schmelzfilmen”, or melting film, was developed by Hexal and has currently four marketed products: olanzapine, sildenafil, donepezil and risperidone [60-62]. Although there are some composition variations between the four formulations, they are mainly cellulose based films. The olanzapine oral film commercially available presents Ethylcellulose as main film forming polymer, plasticized with dibutylsebacate, and apparently according to the patent claims the HPMC is essentially used as gelling agent, although the amounts described may indicate that it can also be used as a film-forming polymer [63-67].

3.15 Others

Additionally, other attention-grabbing technology is Nutra3 Complex®, a fast dissolving strip with a high loading capacity around 250 mg per film. Unfortunately, there are no recent reports regarding this product [68].

Also, FFT Medical presented its own transmucosal drug delivery technology based on a alginate polymeric film, the FFT trans-mucosal film. The company claims that this technology allows delivering a wide variety of substances by a rapid and consistent absorption through the oral mucosa surface directly into the bloodstream. They also refer that the drug dissolution is performed in a controlled rate to avoid the release to the saliva [69].

Additional information about these technology platforms and others are summarized in table 4.

Table 4 – Oral Films’ technology platforms, their owners or developers, related patents and associated marketed products. * – means that there is no specific information about the designation and /or status of the technology / product.

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Commercial products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref.
Buccal Wafer	LTS Lohman	US-07407669 B2	Pfizer	Listerine ® Pocket Packs®		Launched	dispersible		[70, 71]
			McNeil-PPC	Sudafed PE™	Phenylephrine	Discontinued			
			McNeil-PPC	Benadryl ®	Diphenhydramine hcl	Discontinued			
			GlaxoSmithKline	NiQuitin Strips 2.5mg Oral Film	Nicotine	Launched			
VersaFilm™	Intelgenx Technology Corp.		RedHill Biopharma		Rizatriptan film	Approved by FDA	dispersible		[31, 32, 72]
		US-20110136815			Tadalafil film	Phase 2 Clinical Pilot study planed for Q1 2014	dispersible		
					INT0020 Insomnia	Phase 2 Clinical	dispersible		
					INT-0022; anti-psychotic agent	Phase 2 Clinical	dispersible		
					INT-0023 - Allergy	Phase 1 Clinical	dispersible		
					INT-0025 - Prostate hyperplasia	Phase 1 Clinical	dispersible		
					INT0031 Benign Prostatic Hyperplasia	Pilot study	dispersible		
					INT0030 – Animal health Vetafilm	Pilot study	dispersible		
					INT0036 - CNS	Discovery	dispersible		
Thinsol™	Paladin Labs BioEnvelop's™	WO-2009055923					dispersible		[20, 55, 56] [57, 73]

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
Pharmfilm ®	MonoSol Rx LLC	U.S. patent No. 7,824,588	C.B. Fleet Company	Pedia Lax® Quick Dissolve Strips	Sennosides	Discontinued		Polyethylene oxide and HPMC	[14, 20-25] [70],[74-82]
		WO-2011017483	Reckitt Benckiser Pharmaceuticals	Suboxone® Sublingual Film	Buprenorphine Hydrochloride + Naloxone Hydrochloride	Launched	dispersible		
			Prestige Brands	Chloraseptic®	Benzocaine	Discontinued	dispersible		
				Little cold sore throat strip	(Pectin) + Ascorbic acid	Discontinued	dispersible		
		WO-2013019187 WO-2008098151	KemPharm's		Methylphenidate prodrug + ligand	Discovery	dispersible		
		WO-2012040262	MonoSol Rx LLC		Montelukast Sodium	Clinical	dispersible		
			MonoSol Rx LLC		Diphenhydramine hydrochloride	*	dispersible		
			MonoSol Rx LLC		Escitalopram	No Development Reported	dispersible		
			MonoSol Rx LLC		Rizatriptan	Discovery	dispersible		
			MonoSol Rx LLC		Epinephrine	No Development Reported	dispersible		
		WO-2013026002	MonoSol Rx LLC		Testosterone	Discovery			
		WO-2012177326	Midatech MidaSol Therapeutics		Insulin nanoparticles (MidaForm insulin)	Phase 1 Clinical	buccal		
			BiondVax		Multimeric-001	Discovery	dispersible		
		WO-2004066986 WO-2006031209; WO-03030881; WO-2012040262	MonoSol Rx LLC; Vestiq Pharmaceuticals Inc	Zuplenz®	Ondansetron Hydrochloride	Launched	dispersible		
			MonoSol/Midatech		GLP-1 peptides	Discovery	buccal		
		WO-2011124570	APR Applied Pharma; MonoSol Rx LLC; Tesa Labtec GmbH		Zolmitriptan	Launched	dispersible		[83]

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
Rapid Dissolving Film	Kyukyu Pharmaceutical Co Ltd	WO-2005117803; WO-2011108643; WO-09917753	Kyukyu Pharmaceutical Co Ltd; BIOMEDIX.CO.,LTD	Amlodipine OD Film	Amlodipine Besilate	Launched	dispersible		[33], [34, 84- 88]
				Voglibose OD Film	Voglibose	Launched	dispersible		
					Loperamide	Launched	dispersible		
				Olopatadine Hydrochloride OD Film	Olopatadine Hydrochloride	Discovery	dispersible		
				Donepezil Hydrochloride OD film	Donepezil Hydrochloride	Launched	dispersible		
				Zolpidem Tartrate OD Film	Zolpidem Tartrate	Launched	dispersible		
				Loratadine OD Film	Loratadine	Launched	dispersible		
				Waplon	Triamcinolone Acetonide		dispersible		
Adhesive and Disintegrating Film (ADF)		US 20040126330 A1 WO-03026654	Kyukyu Pharmaceutical Co Ltd		Nicotine	Discovery	buccal		[89]
					Fentanyl	Phase 2 Clinical	buccal		

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
Dissolvable Film Technology RapidFilm®	ARx		Novartis Consumer Health	Gas-X®	Simethicone	Launched	dispersible	PVA Starch Medium MwPEG	[70]
				Theraflu®Thin Strips®	Dextromethorphan	Discontinued	dispersible		
				Triaminic® Thin Strips®	Phenylephrine	Discontinued	dispersible		
	Labtec GmbH / APR Applied Pharma Research	WO-2008040534; WO-2009043588	Norgine (Europe and Middle East, Africa and Australasia) / SciClone Pharmaceuticals, Inc (China and Vietnam) / Takeda Canada (Canada) / Monosol RX §	Setofilm® / Ondansetron Rapidfilm® / Ondissolve™	Ondansetron Hydrochloride	Launched	dispersible		[20], 75, [90, 91],[92, 93]
							dispersible		
							dispersible		
							dispersible		
		WO-2011124570	APR Applied Pharma Research SA; MonoSol Rx LLC; tesa Labtec GmbH	Zolmitriptan ODF RapidFilm®	Zolmitriptan	Launched	dispersible		[94, 95]
				Aripiprazole ODF	Aripiprazole	No Development Reported	dispersible		
		WO-2012110222	APR Applied Pharma Research SA; tesa Labtec GmbH	Olanzapine ODF	Olanzapine	Registered	dispersible		[96]
		WO-2009043588; EP-02213278	APR Applied Pharma Research SA; Ferrer Internacional SA; tesa Labtec GmbH	Donepezil ODF	Donepezil	Registered	dispersible		[97]

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
Schmelzfilm	Hexal Pharmaceuticals	WO-2007009801		Olanzapin HEXAL® SF Schmelzfilm	Olanzapine	Launched	orodispersible	Ethylcellulose HPMC	
		WO-2007009800		Anti-migraine		*			
		WO-2010115724		Aripiprazole HEXAL® SF Schmelzfilm	Aripiprazole	*	orodispersible		
			Hexal Sandoz	Risperidon HEXAL® SF	Risperidon	Launched	orodispersible		[98]
				Donepezil-HCl Hexal® SF	Donepezil	Launched	orodispersible		
		WO-2012055947		SildeHEXAL SF (Tornetis)	Sildenafil	Launched	orodispersible		
BEMA™	BioDelivery Sciences International (BDSI)	WO-03086345	KunWha Pharmaceutical Co Ltd; Meda AB; TTY Biopharm Co Ltd	Onsolis®	Fentanyl	Launched	Buccal	Backing layer – HPC, HEC Active layer – polycarbophil and NaCMC	[99-101]
		WO-2008011194; WO-2007070632	BioDelivery Sciences International Inc	BEMA® Granisetron	Granisetron	Discovery	Buccal		
		WO-2013096811; WO-2010008863	Endo Pharmaceuticals	BEMA® Buprenorphine	Buprenorphine	Phase 3 clinical	Buccal		
				BUNAVAIL™	Buprenorphine + Naloxone	NDA submitted to FDA on July 2013	Buccal		
		WO2005016321	BioDelivery Sciences International Inc	BEMA® Triptan	Triptan	Discovery	Buccal		[102]
			Arius Pharmaceuticals Inc	BEMA® Zolpidem	Zolpidem	No Development Reported	Buccal		

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products			Oral Film Type	Polymer	Ref	
					Drug substance (if any)	Phase / Status				
Fast dissolving Film PharmaForm technology	Hughes Medical Corp						dispersible		[20]	
	Auxilium Pharmaceutic als	WO-2010002418	Rotavax™	Rotavirus	phase II clinical trials (May 2013)		Buccal		[50, 51, 103, 104]	
				Testosterone	Discontinued		Buccal			
		WO-2009151574		Oxybutynin	No Development Reported		Buccal			
				Fentanyl	No Development Reported		Buccal			
Soluleaves™	Bioprogress	WO-2006114604 (A3)	Meldex International	Nicotine	No Development Reported		Buccal	Cellulose derivative	[20, 54]	
Bio-FX Fast- Onset ODF	NAL Pharma	WO-2010062688		Selegiline	Discovery		dispersible		[46, 105]	
				Rizatriptan Benzoate	Phase 1 Clinical					
				Nicotine	Discovery					
				Levocetirizine	Discovery					
				Zolmitriptan	Discovery					
				Sumatriptan	Discovery					
				Sildenafil citrate	Phase 1 Clinical					
				Tadalafil	Discovery					
				Montelukast	Discovery					
				Fentanyl	Discovery					
				Cetirizine HCl	Discovery					
				Donepezil	Discovery					
	Zolmitriptan	Discovery								

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
SmartFilm®	Seoul Pharma Co Ltd	WO-2013129889	Pfizer Inc	Vultis®	Sildenafil citrate	Launched	dispersible		[35, 36, 38]
					SPO-1202 Attention deficit hyperactivity disorder	Discovery			
					SPO-1201 Depression	Discovery			
					SPO-1113 Schizophrenia	Discovery			
					SPO-1108 Asthma	Discovery			
					SPO-1112 - Dementia	Discovery			
Quicksol®	SK Chemicals Co Ltd	WO-2013100564	SK Chemicals Co Ltd		Montelukast	Launched (Korea) Initiated EU development	dispersible		[47, 106, 107]
					Mirodenafil hydrochloride	Launched			
Orally Rapid Disintegration Film	AstraZeneca plc	WO-2013085276		Anastrozole ODF	Anastrozole	Phase 1 Clinical completed	dispersible		[108, 109]
Thin film	NeuroHealing Pharmaceuticals Inc	WO-2006078998			Tropicamide	Phase 2 Clinical	Buccal	Pullulan	[58, 59, 110]
Eluting Bandage Platform	Pharmedica	WO/2012/104834			Insulin	No Development Reported	Buccal		[111] [52]
					Cannabinoids	No Development Reported	Buccal		
Fast-onset sublingual bilayer film	Cynapsus Therapeutics	WO-2012083269; WO-2010144817	Cynapsus Therapeutics	APL-130277	Apomorphine	Phase 1 Clinical	dispersible bi-layer sublingual	Cellulose (HEC?) and / or modified starch (MDX)	[49, 112, 113]

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
Transmucosal Matrix Patch	ElSohly Laboratories, Inc				Dronabinol	Discovery	buccal		[114]
*	Aoxing Pharmaceutical				Midazolam maleate	No Development Reported	dispersible		[115]
					Naloxone	No Development Reported	Sublingual		[116]
*	CHA Bio & Diostech Co Ltd	WO-2010151020							[117]
		WO-2012121461			Montelukast sodium	Pre-registration	dispersible		[118]
		WO-2014025206			Aripiprazole				[119]
Oral thin film	CTC Bio Inc	WO-2013002578			Clomipramine	Pre-registration	dispersible		[120-122]
					Tadalafil	Clinical	dispersible		
					Donepezil	Clinical	dispersible		
					Sildenafil	Launched	dispersible		
		WO-2012108738	CTC Bio Inc; Dong Kook Pharmaceutical Co Ltd; Huons Co Ltd; Jeil Pharmaceutical Co Ltd; Jin Yang Pharm Co Ltd; KunWha Pharmaceutical Co Ltd						
Oral thin Film	CURE Pharmaceutical Inc		CURE Pharmaceutical Inc	PediaSUNATE™	artesunate and amodiaquine	Discovery			[123]
Trans-mucosal Drug Delivery	FFT Medical	WO-2007073346			Adrenaline	Pre-clinical		Film-forming agent comprising an alginate salt of monovalent cation	[11, 69, 124]
					Cancer Pain	Pending/under negotiation			
					Erectile Dysfunction	Out-licensed			
					Migraine	Out-licensed			
					Parkinson's disease	Under development			
		WO-2013143891			NRT / Nicotine	Out-licensed			[125]

Brand name / Designation	Owner / Originator Company	Patent (s)	Active Companies / Partner / Distributor	Products	Drug substance (if any)	Phase / Status	Oral Film Type	Polymer	Ref
Oral Dispersible Film	Aavishkar			Tadalafil	Tadalafil	Launched			[126]
				Ondansetron Hcl	Ondansetron Hcl	Launched			[126]
				Simethicone	Simethicone	Launched			
				Dextromethorphan Hbr Phenylephrine Hcl 2.5 mg Strips (Cough & Cold)	Dextromethorphan Hbr Phenylephrine Hcl 2.5 mg	Launched			
				Vitamin B12 strips	Vitamin B12	Launched			
				Vitamin D3 strips	Vitamin D3	Launched			
				Electrolyte Strips	Vitamin B12 + Vitamin C + Sodium + Potassium	Launched			
				Energy strips	Caffeine + Vitamin B12 + Vitamin E + Vitamin B6+ Biotin+ Vitamin B5	Launched			
				Melatonin Strips	Melatonin	Launched			
				Teeth Whitening Strips	6% Hydrogen Peroxide	Launched			
				Breath Freshening Strips		Launched			
					AVISH-01 (AIDS) AVISH-02 (Vaginal infections)	Discovery R&D completed			[11]

4 Market overview

The feverous need of launching on the market renewed drug delivery systems of already approved drugs, in order to avoid generic competition, allied with the increased patient's compliance concern, have driven the attention of the industry for the orodispersible technology. There are enormous costs and time consumption in the discovery and development of new chemical entities and at the same time there is a real need to improve the efficacy, safety and compliance of some marketed products [127]. In fact, almost a quarter of the drugs in the market do not provide the expected commercial returns due to its poor bioavailability and undesirable pharmacokinetics, demanding the development of innovative, better and suitable drug delivery systems [128]. Therefore, the field of novel drug delivery technologies is highly competitive, but also very rewarding. The average cost of a new formulation is considerable lower than the cost involving the development of a new chemical entity, in about 40 million dollars, and generally takes also less time to develop (approximately 4 to 5 years). Actually, the changing market trends are very clear, the FDA approvals revealed a majority of reformulations or combinations of current approved products, in contrast with the 25% of new drugs approvals. In 2012, the total drug delivery market (DD) worth \$142.5 billion [4], and presently, for the 10 most-popular DD technologies, its estimated market value of \$81.5 billion [129] and is expected to achieve \$92 billion by 2016 [130].

The oral formulations are the number-one segment of the drug delivery, retaining more the larger sliver of the global market share [129]. The orodispersible drug delivery systems have found its space as mainstream pharmaceutical products. In fact, eight in ten patients prefer orodispersible dosage forms over the traditional solid oral dosages. Orodispersible films initially emerged as an option for rapid drug delivery, and later with the buccal films as an alternative for low bioavailability drugs. From the market standpoint, oral films were immediately appointed as a successful delivery system probably fueled by the huge success of Listerine® Pocket Packs®. Actually, oral films proved to be a rewarding commercial platform with a growing rate of 500 million dollars by year since 2006 and reached the 2 billion dollars in 2010 [20]. Recent market analyses revealed that the oral film manufacturers have had rapid revenue growth from 2009-2014 and a similar trend is expected at least until 2019. It was estimated an annual growth of 17,1% in the same period for this sector [18]

In 2001, Pfizer launched the Listerine® Pocket Packs® in the market, the first commercial oral film and a blockbuster that in one year exceeded 175 million dollars [9]. Nowadays, under new ownership, it still remains a viable business, although it is a shadow of its initial success. In 2003, Chloraseptic® Relief Strips, the first drug substance loaded oral thin film reached the market [131]. Chloraseptic® Relief Strips with benzocaine provided an immediate and convenient relief of sore throat pain. In 2004, Novartis debuts in the oral film market with Triaminic® Thin Strips and Theraflu® Thin Strips to treat the most common symptoms of a cold in young children (ages 6-12) and older children (> 12 year old) or adults, respectively. These products were considered the "Best Product of 2004" only three weeks after their official launch, however, they are no longer available in the shelves [132]. The melts-in-mouth portable delivery platform, with an easy and pleasant administration for children was probably the first multi-symptom cough and cold medicines that provided a fast and accurate dosing. In the beginning of 2012, Novartis decided to discontinue the manufacturing and distribution of Children's Triaminic® Thin Strips "after a careful consideration" [133]. Novartis claimed that this decision was based upon a business need, but there are some suggestions that the removal of these products included production issues and poor sales [134, 135]. The latter may probably be a reflection of the decline in the consumption of cough and cold medications due to the implementation of restrictions in 2007 [136, 137].

Nevertheless, Novartis and Pfizer as marketing partners remain as top players in the thin film industry, their capitalization in these success brand products allowed them to gain a strong position in the field [138]. The thin film industry exhibits a high level of competition, but until 2010 no prescription oral film product had reached the market. It was a slow ride from the over-the-counter (OTC) market until the first prescription has been approved.

It was only in 2010 that the first Rx oral film, the ondansetron Rapidfilm® (Setofilm®) and the ondansetron Pharmfilm® (Zuplenz®), received European and FDA approval, respectively. Labtec GmbH, APR Applied Pharma Research SA (APR) and MonoSol Rx LLC (MonoSol) entered in the market with an ondansetron oral thin film for the prevention of nausea and vomiting, staunch that would capture a broad share of an appellative market that generated 1.9 billion dollars in the same year [139]. A month after Zuplenz® launch, MonoSol together with Reckitt Benckiser Pharmaceuticals received FDA approval for Suboxone® sublingual film [135, 140]. This thin film, with two drug substances, buprenorphine and naloxone, approved for the treatment of opioid dependence in adults, was a huge success contributing to boost the oral films market. In 2011, Suboxone® thin film recorded sales of 513 million dollars and accounted for 96 percent of the oral transmucosal film market [141]. In 2012, US sales of Suboxone® sublingual film alone exceeded 1.5 billion dollars and continue with gradual growth [142]. During clinical trial the patients seemed to prefer the Suboxone® sublingual film rather than Suboxone® sublingual tablets, due to its fast dissolution and more pleasant taste profile [140]. These factors attracted other companies, as Alvogen Pine Brook, Actavis, Intelgenx and BioDelivery Sciences International (BDSI) to develop similar technologies. In fact, the first three companies have recently filled abbreviated new drug applications (ANDA) for generic products of Suboxone® sublingual film whereas BDSI submitted a NDA with its own buccal film technology, the BUNAVAIL™. BDSI believes that BUNAVAIL™, which adheres to the inside of the cheek, has the potential to offer advantages over Suboxone® sublingual film [43, 142].

At the moment, none of these competitors' products are on the market since a patent infringement lawsuit against these applicants was submitted by Reckitt Benckiser [143]. The success of the Reckitt Benckiser's prescription thin film proved the viability and value of this pharmaceutical form in the Rx market. In the US the oral films had come into a strong prominence and the prescriptions confirm the preference of these pharmaceutical forms [144].

5 Market outlook

It is evident the increasing consumer acceptance of thin films and the market success that can be achieved. Generally, for this dosage form the OTC market is the preferred due to the close proximity with the consumer and the easily advertising. Additionally, in the USA market the convenience store category is extremely important and it has a high sales impact. There are more than 140,000 stores across the US, which achieved a gross sale of 708.2 billion dollars in 2012, with a continuous sale grew every year. Regarding the OTC products, in the Convenience Store News 2013 Industry Report, they are included as health and beauty care products, which in overall had an average gross margin of about 46.89 percent in 2012 [20, 145]. It is a very tempting market that may lead to precipitated launches that sometimes may fail the expectations. As example of that, the Sudafed PE™ Quick Dissolve Strips was launched by Pfizer in the middle of 2005, for the relief of sinus pressure and congestion [146, 147]. The brand sales were probably lower than expected due to the intense competition in the cough-and-cold products segment. In fact, considering only Triaminic® and Theraflu®, launched two years earlier, Sudafed PE™ effectively did not leverage a strong point-of-difference, not even in the price (Sudafed PE™ approximately 0,45\$/film and Triaminic approximately 0,5\$/film) [132, 148]. In addition, it should be mentioned also that this segment sale were also off due to the implementation of some constraint measures for cough-and-cold medicines administration.

Nevertheless, all this background experiences are important for planning and develop new oral film. It is crucial to consider that the market success of a new oral film depends on its capacity of differentiate from its competitive set, beyond an attractive new dosage form. A product can achieve a decisive point of difference by its unique characteristics which may engage the customer's attention and bring also some significance. Therefore, considering the Rx market, it would be wise to deliver innovative drug substances, or others that bring additional value, to the oral film platform, otherwise it will be difficult to achieve success.

The manufacturing process of the oral films, when comparing with some complex oral delivery systems, is cost-effective and generally results in affordable end-products [20]. However, the majority of the oral films is more expensive than conventional oral dosage forms and may not represent a clear benefit for the consumer. It should be reminded that once the form novelty wears off, it must be found a way to gain advantage over the other competitors / brands that do equal efforts for offering equivalent products.

On the other hand, considering the previous discussion, there is still a poorly explored market with this delivery platform, the veterinary market. It is well known that in general the animals tend to reject, spit out or vomit conventional dosage forms. In fact, giving oral medications to pets can be sometimes a dangerous practice, which can also reduce even the owner compliance, and compromise the treatment. It was evaluated the overall owner-perceived acceptability and the easiness administration of an orodispersible film compared with gelatin capsules in cats. Although there were no significant differences in the general acceptability of the owners, it was shown that the orodispersible films facilitated significantly the administration of the medication [149, 150]. Currently, few companies have developed oral films applied to this segment, and the available products are scarce and limited to OTC products based on blends of herbal extracts [151, 152]. Additionally, IntelGenx presents in its pipeline the VetaFilm which rapidly hydrate and adheres upon contact with the tongue. It cannot be spit out and offers appealing flavors and scents to increase the acceptability in pets [31].

The veterinary industry includes several health products such as biologicals, medicated feed additives and veterinary pharmaceuticals that deals with a wide range of products: metabolic drugs, anti-infectives, reproductive aids, feed additives, vaccines, imaging diagnostics, topical solutions, parasite controls, oncologic, cardiovascular, and osteoarthritis drugs [153].

It is estimated that the global animal health care market is worth between 92 and 102 billion dollars [154]. Regarding pets, there is an evident trend of the owners spending more money each year on their pets' health. In the US, it is expected that pet-owners spending will reach 33 billion dollars in 2014. This market segment will always be far from recession, driven by the idea that pets are considered family members. Besides that, the farm animals' health has been in the spotlight as a result of growing awareness of the impact that animal health may have in the human food safety and public health. The current unmet animal health needs, especially in animal disease surveillance, vaccines and lack of drugs in the senior animal veterinary care market (oncology, cognitive dysfunction syndrome, antidepressants) may also fuel the veterinary market growth [153]. Although, US remain the largest regional market for animal medication, Asia-Pacific is the fastest growing regional market. Regarding the products segment, the nutritional chemicals and parasiticides have the majority share in the total dollar sale, whereas vaccines and diagnostics are the fastest growing products segments [155, 156].

It is clear that animal health is far to be little and insignificant health care niche. Actually, keeping pets and farm animals healthy might be a huge business. Therefore, innovative delivery platforms such as the orodispersible films, that quickly dissolve and become sticky in contact with saliva, can easily become valued by pet owners and animal caregivers.

Another unexplored market with these technology platforms is the biologics products. There are some references and efforts in the development of these type of products especially in immunotherapy, but at the moment no product had already reached the market. For example, vaccines in oral film formulations may have significant advantages. Despite of the needle free delivery, which may increase patient compliance, the higher stability may simplify the worldwide storage and distribution. The simplification of the logistic would also favor the mass immunization campaigns [157, 158]. In fact, this type of small and stable vaccines could be easily sent by mail. Furthermore, it is expected that the human vaccine industry forecast reaches 41.85 billion dollars by 2018 [159], with a CARG growth of 62.81 percent from 2013 to 2018 [160].

In addition to the quick-dissolving oral film influenza vaccine, under development by BiondVax - MonoSol Rx, others had already reported the development of oral film vaccines. During 2007, Johns Hopkins students had reported the development of an oral film vaccine, the rotavirus thin film delivery system which may surpass the drawbacks of the liquid vaccine. The original idea came from Aridis Pharmaceuticals that owns the rotavirus vaccine stable at room temperature and gave the challenge to the researchers from the Johns Hopkins School of

Medicine. The oral film system is composed by a FDA-approved biocompatible polymer, which is pH-responsive. This composition design avoids the degradation of the vaccine in the stomach acid, allowing its release in the small intestine, triggering the immune response. According to their patent application these pH-sensitive microparticles are composed by a complex polymeric mixture, a copolymer of methacrylic acid or acrylic acid, as an Eudragit®- like copolymer, a pluronic polymer, a chitosan or a derivative or a combination thereof; and possible additional components as a surfactant, a sugar, a buffering salt and or a combination thereof [104]. The Eudragit® polymers are an Evonik Industries AG trademark that offer a full flexibility of pH-dependent drug release [161]. In fact, the manufacture method to prepare these microparticles includes the blend of two different grades of Eudragit®, possibly to accurately define the pH release of the drug. An anionic copolymer of methacrylic acid with ethyl acrylate is balanced with an anionic copolymer of methacrylic acid with methyl methacrylate, so the drug release pH may be achieved somewhere between 5.5 and 7. The oral film composition is based on water-soluble polymers, as PVP or PVA, mucoadhesive polymers, as PEO and / or sodium alginate. Therefore, this composition allows that Rotavax™ vaccine melts quickly in a children's mouth, prompting them to swallow it. Unfortunately, no additional developments had been reported since then [20, 162]. Currently, the Johns Hopkins School of Medicine also has a clinical trial ongoing to evaluate the Safety and Efficacy of a sublingual dissolving film for Peanut Allergy. The estimated date for the completion of the study is in the beginning of 2015 and it is expected that this sublingual immunotherapy with a dissolving peanut extract film has the potential to improve the efficacy of this type of treatment [163, 164].

It has been an increasing interest in the development of micro- and / or nano- drug delivery systems associated to buccal polymeric matrices for a transmucosal delivery [165-171]. These nanoparticle systems for oral absorption have been recently explored to incorporate poorly soluble drugs, to extend and improve the buccal release, to provide an improvement in the drug targeting and also to increase drug stability. These systems generally include nanosuspensions [166, 167, 169], nanofibrous matrix system [168], solid lipid nanoparticles [165, 171], PEG-b-PLA nanoparticles [171], submicron and nanosized particles of lysozyme (Lys)-loaded d,l-valine (Val) [170]. The majority of these studies were initially applied to the proteins, especially due to its large size, low oral bioavailability and poor stability, but they are currently extended to non-biologic drugs. Nevertheless, for the development of this type of systems it is important to consider the size of the coating particles. The size and shape of the particles may lead to undesirable aggregation and loss in the homogeneity, which could compromise the physical stability of the films in terms of both mechanical and mucoadhesive properties.

6 Conclusion

The main catalysts of the drug-delivery market are the patent cliff and more informed and autonomous consumers [4]. Therefore, the demand side for pharmaceutical treatments has been changing and nowadays the approach is more patient - centered and quality- based.

Recent reports refer that in the next five-year period, many oral film drug producers will focus on extend their drug pipeline through other therapeutic classes [18]. At the same time it is expected that the formulation complexity may contribute to technical, manufacturing and regulatory barriers that may lessen the growth of the oral film market [4]. So, it is critical that the value added by any new delivery platform boosts its own growth by the continuous improvement of consumer compliance and by enticing new consumers.

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