Journal of Controlled Release 206 (2015) 108–121

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Oral films: Current status and future perspectives II — Intellectual property, technologies and market needs

Ana Filipa Borges [a,b], Cláudia Silva [a], Jorge F.J. Coelho [c], Sérgio Simões [a,b]

[a] Bluepharma, Indústria Farmacêutica, S.A., Portugal
[b] Faculty of Pharmacy, University of Coimbra, Portugal
[c] CEMUC, Department of Chemical Engineering, University of Coimbra, Portugal

Contents

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 with 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 the 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

http://dx.doi.org/10.1016/j.jconrel.2015.03.012

developments. There is also an increase in the 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 Lohmann 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 (Fig. 1). As already described in 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.

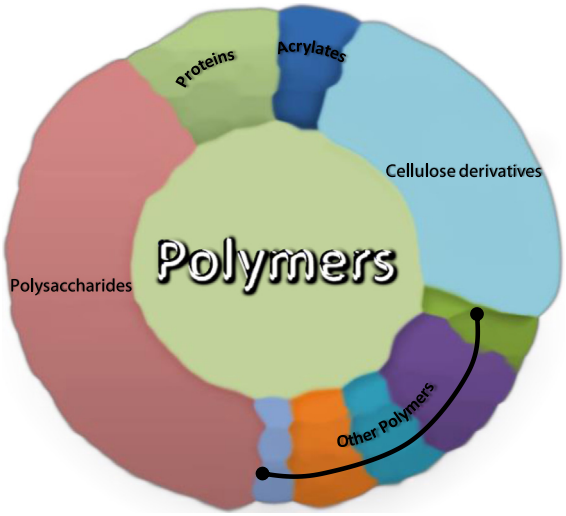

Fig. 1. Overall scenario of polymers usage. The polysaccharide group comprises starch derivatives, pectin, gums, dextrans and alginates; other polymers group includes polyvinyl and polyethylenoglycol polymers and co-polymers; the protein group consists of soy proteins, casein, zein, collagen and others; the acrylate group refers mainly to methacrylate

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, 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) is common. 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 in Table 1 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 other drug substances such as montelukast sodium, rizatriptan, escitalopram oxalate, donezepil 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.

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 1).

3.3. VersaFilm™

VersaFilm™ technology was developed and patented by IntelGenx Technologies Corp. Initially developed as an edible film for the instant delivery of savory flavors 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 s to 10 min, and it can be sublingual, depending on the intended application. The maximum drug load claimed is around 40 mg. 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 has 2 different technologies the “Orally Disintegrating Film”, which dissolves in 10 to 30 s and the “Adhesive and Disintegrating Film” that adheres to the oral mucosa and the disintegration time can vary between 30 min and 8 h [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 140.45 mg 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 Sidenafil SmartFilm® technology is a fast dissolving film composition 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 of a bioerodible polymer film which adheres quickly to the oral mucosa (less than 5 s) 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 min. 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 layers are composed by hydroxypropyl cellulose and 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 specially 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 its incorporation in a film difficult. Therefore, the apomorphine non-neutral form is loaded in one film layer, and a neutralizing agent is incorporated in another film layer, physically separated from each other. The neutralizing agent's layer dissolves quickly upon contact with saliva, allowing a

ble 1
al 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 Lohmann	US-07407669 B2	Pfizer	Listerine ® Pocket Packs®		Launched	Dispersible		[70,71]
			McNeil-PPC	Sudafed PE™	Phenylephrine	Discontinued			
			McNeil-PPC	Benadryl ®	Diphemhydramine hcL	Discontinued			
			GlaxoSmithKline	NiQuitin Strips 2.5 mg oral film	Nicotine	Launched			
VersaFilm™	Intelgenx Technology Corp.		RedHill Biopharma		Rizatriptan film	Approved by the FDA	Dispersible		[31,32,72]
		US-20110136815			Tadalafil film	Phase 2 clinical pilot study planned 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		[20,55–57,73]

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		

(continued on next page)

Table 1 (*continued*)

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.
			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]
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]
			MOCHIDA PHARMACEUTICAL CO., LTD.	Voglibose OD film	Voglibose	Launched	Dispersible		
		WO-2010023874	Kyukyu Pharmaceutical Co Ltd		Loperamide	Launched	Dispersible		
			Kyukyu Pharmaceutical Co Ltd; Maruho Co.,Ltd.	Olopatadine Hydrochloride OD Film	Olopatadine Hydrochloride	Discovery	Dispersible		
		WO-2013121663	Kyukyu Pharmaceutical Co Ltd; Elmed Eisai co.,ltd.	Donepezil Hydrochloride OD film	Donepezil Hydrochloride	Launched	Dispersible		
			Mochida Pharmaceutical Co Ltd	Zolpidem Tartrate OD Film	Zolpidem Tartrate	Launched	Dispersible		
			Mochida Pharmaceutical Co Ltd Teva Pharma Japan Inc.	Loratadine OD Film Waplon	Loratadine Triamcinolone Acetonide	Launched	Dispersible Dispersible		
Adhesive and disintegrating film (ADF)		US 20040126330 A1 WO-03026654	Kyukyu Pharmaceutical Co Ltd		Nicotine	Discovery	Buccal		[89]
Dissolvable film technology	ARx		Novartis Consumer Health	Gas-X®	Simethicone	Launched	Dispersible	PVA	[70]
				Theraflu®Thin Strips®	Dextromethorphan	Discontinued	Dispersible	Starch	
				Triaminic® Thin Strips®	Phenylephrine	Discontinued	Dispersible	Medium MwPEG	
RapidFilm ®	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 Dispersible Dispersible Dispersible		[20,75,90–93]
		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]
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	Backing layer — HPC, HEC	

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.