Drug Delivery

ISSN: 1071-7544 (Print) 1521-0464 (Online) Journal homepage: http://www.tandfonline.com/loi/idrd20

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To cite this article: Jessica Silva Barbosa, Filipe A. Almeida Paz & Susana Santos Braga (2016) Montelukast medicines of today and tomorrow: from molecular pharmaceutics to technological formulations, Drug Delivery, 23:9, 3257-3265, DOI: 10.3109/10717544.2016.1170247

To link to this article: http://dx.doi.org/10.3109/10717544.2016.1170247

Accepted author version posted online: 24 Mar 2016.
Published online: 11 Apr 2016.

Drug Delivery

http://informahealthcare.com/drd
ISSN: 1071 7544 (print), 1521 0464 (electronic)

Drug Deliv, 2016; 23(9): 3257 3265
 DOI: 10.3109/10717544.2016.1170247

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REVIEW ARTICLE

Montelukast medicines of today and tomorrow: from molecular pharmaceutics to technological formulations

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Abstract

Montelukast sodium is a leukotriene antagonist of growing interest as an alternative therapy for asthma across different age groups due to its bronchoprotective, anti-inflammatory and anti-allergic properties. Currently, montelukast is commercialized only in oral solid dosage forms, which are the favorite of adult patients but may pose challenges in administration to children of young age or patients suffering from dysphagia. This review presents a comprehensive revision of scientific reports and patents on emerging strategies for the delivery of montelukast. A common ground to these reports is the pursue of an enhanced montelukast performance, by increasing its bioavailability and physico-chemical stability. A wide variety of strategies can be found, from the formation of supramolecular adducts with cyclodextrins to encapsulation in nanoparticles and liposomes. The new dosage forms for montelukast are designed for non-enteric absorption, some for absorption in the oral cavity and another two being for local action in the nasal mucosa or in the pulmonary epithelium. The review describes the emerging delivery strategies to circumvent the current limitations to the use of montelukast that are expected to ultimately lead to the development of more patient-compliant dosage forms.

Keywords

Chronotherapeutic systems, cyclodextrins, drug stability, nano-encapsulation, oral delivery

History

Received 2 February 2016
Accepted 20 March 2016

Introduction

The discovery in 1979 of the implication of leukotrienes in the etiology of respiratory diseases and the elucidation of their structure triggered the search for novel compounds able to block leukotrienes as new treatments for asthma. For over a decade, the company Merck Frosst developed two research programs on the topic, one to find an inhibitor of the key biosynthesizing enzyme, 5-lipoxygenase, and the other to find a selective blocker of the Leukotriene D4 receptor. These projects yielded six compounds, which were brought into human clinical trials and ultimately led to the release of montelukast (Figure 1) under the tradename Singulair. Today, montelukast treats millions of patients around the world with market sales estimated around 5 billion US dollars per year (Young, 2011).

Asthma, a chronic inflammation manifesting as shortness of breath, wheeze and chest tightness (Pawankar, 2014; Global Initiative for Asthma (GINA), 2015) is raising concerns in public health due to the increase in the incidence of cases over the last decades. The respiratory airways present hyperresponsiveness (AHR) to external stimulus and bronchoconstriction due to subepithelial fibrosis and smooth muscle hypertrophy and hyperplasia, which reduce the ventilation capacity of these airways (Lemanske & Busse, 2003; Adcock et al., 2008; Kudo et al., 2013; Global Initiative for Asthma (GINA), 2015).

These pathophysiological alterations are triggered by inflammation mediators, such as cysteinyl leukotrienes (CysLTs) C4 (LTC4), LTD4 and LTE4 that activate the cysteinyl-leukotriene 1 receptors (CysLT1Rs) existing in bronchial smooth muscle (Hamid et al., 2003; Wenzel, 2003). By blocking CysLT1R (Figure 2), montelukast is able to restore normal functionality and consequently improve lung function (Wenzel, 2003; Adcock et al., 2008). Montelukast has also anti-allergic action, thus protecting against allergen-induced asthma and preventing exercise-induced asthma (Leff et al., 1998; Phipatanakul et al., 2002).

Marketed montelukast formulations

Montelukast is generally well tolerated by patients and it is suitable for incorporation into oral dosage forms (Knorr et al., 1998; Pizzichini et al., 1999; Storms et al., 2001; Chorao et al., 2014). Noteworthy, this approach was a major improvement in drug administration when compared to the classic medicines for asthma treatment such as corticosteroids and bronchodilating agents, available only as inhalables.

In its original neutral form, montelukast is poorly soluble in water (0.2 0.5 μg/mL, 25 °C), with overall solubility increasing to 100 1000 μg/mL through the formation of a sodium salt, which is the commercialized form of this API.

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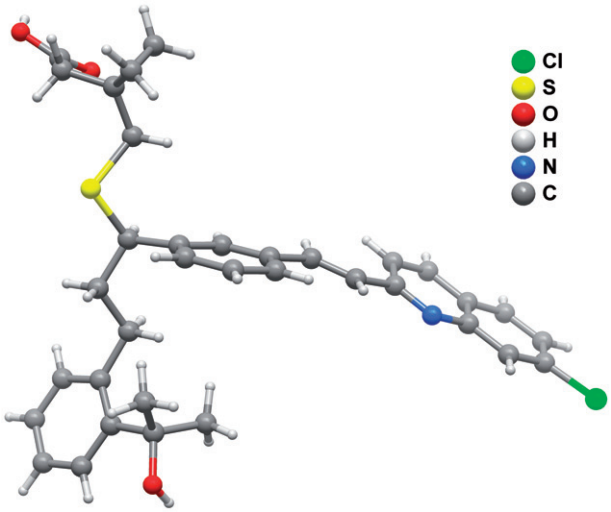

Figure 1. Molecular representation of montelukast (acid form). Redrawn from the atomic coordinates of the crystal structure of montelukast (Thun et al., 2009), available at the Cambridge crystallographic database (©CCDC 2002 2016).

Currently available dosage forms

Presently, montelukast sodium is available from a variety of pharmaceutical companies, either under the tradename Singulair® (by Merk) or as a generic API. The formulations are to be taken orally and comprise only solid dosage forms, namely tablets, chewable tablets and oral granules (Table 1).

Uses and limitations

The most important limitations to the use and formulation of montelukast are associated with its physico-chemical properties. Montelukast, both in the neutral and the salt form, is sensitive to light, temperature, humidity and oxidation (Al Omari et al., 2007; Okumu et al., 2008; Rashmitha et al., 2010). In this context, the presently available dosage forms are designed to minimize exposure to light and humidity, which explains why liquid formulations are not marketed to date.

Administration of montelukast to small babies is a challenge. The available formulation is the granules with compatibility guaranteed only for mixtures with the mother's milk or milk formulas, after which they should be quickly administered. Furthermore, the oral granules have to be packed in individual, light- and air-proof sachets and, after opening, they should be ingested within 15 minutes. In the case of the chewable tablets, some formulations (including Singulair) contain aspartame as sweetener. Being thus a phenylalanine source aspartame-containing tablets are not recommended for patients with phenylketonuria (Merck & Co, 2015).

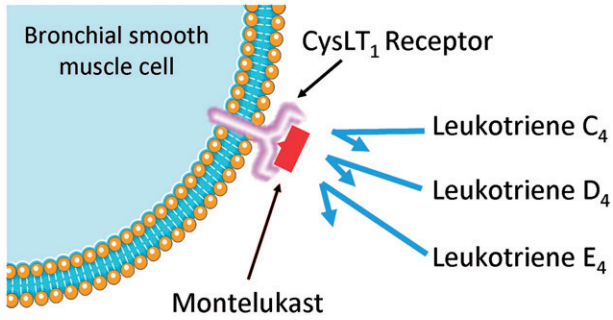

Figure 2. Interaction of montelukast with CysLT1R blocks the access to the active site for CysLTs, which are no longer able to trigger inflammation.

Pharmacokinetics from oral administration

Oral administration of montelukast implies that not all the dose contained in the tablet or granules reaches the bloodstream, due to losses during gastroenteric absorption and the effect of hepatic first pass metabolism, known to be the major cause of its relatively low bioavailability (61 73%, depending on the dose and on the concomitant food intake) (Cheng et al., 1996).

Montelukast undergoes extensive oxidative metabolism in the liver by the cytochrome P450 enzyme system, with a very significant contribution of the mono-oxidase CYP2C8 (72%), followed by CYP3A4 (16%) and CYP2C9 (12%), and it is excreted into the bile (Cheng et al., 1996; Filppula et al., 2011). Its permanence in the bloodstream is relatively short. Its plasmic concentration peaks at around 2 to 4 h after intake and it has a rapid elimination. The mean plasma half-life is of 2.7 to 5.5 h (Kearns et al., 2008).

Adverse reactions & drug interactions

Montelukast is generally well tolerated, although adverse reactions were reported, with stronger incidence in infants: headache, diarrhea, abdominal pain, nausea, fever and cough (Knorr et al., 1998; Lipworth, 1999; Simons et al., 2001; Storms et al., 2001; van Adelsberg et al., 2005). In adults, cases of hypersensitivity have been reported, leading to autoimmune vasculitis, hepatic eosinophilic infiltration and even anaphylaxis (Calapai et al., 2014).

Reported drug interactions with montelukast refer to the reduction, by up to 40%, of its plasmic concentration when it

Table 1. Marketed formulations of montelukast, their doses, benefits and target age groups.

Dosage	Formulation	Benefits	Age group
4 mg	oral granules	Easy to swallow, dispersible and compatible with lactant's milk[a,b]	6 months to 5 years
	chewable tablets	Suitable for youngsters[b,c]	2 5 years
5 mg	chewable tablets	Suitable for youngsters[b,c]	6 14 years
10 mg	film coated tablets	Resistant to daylight[b,c]	≥15 years

[a]Migoya et al. (2004).
[b]Storms (2007).
[c]Al Omari et al. (2007).

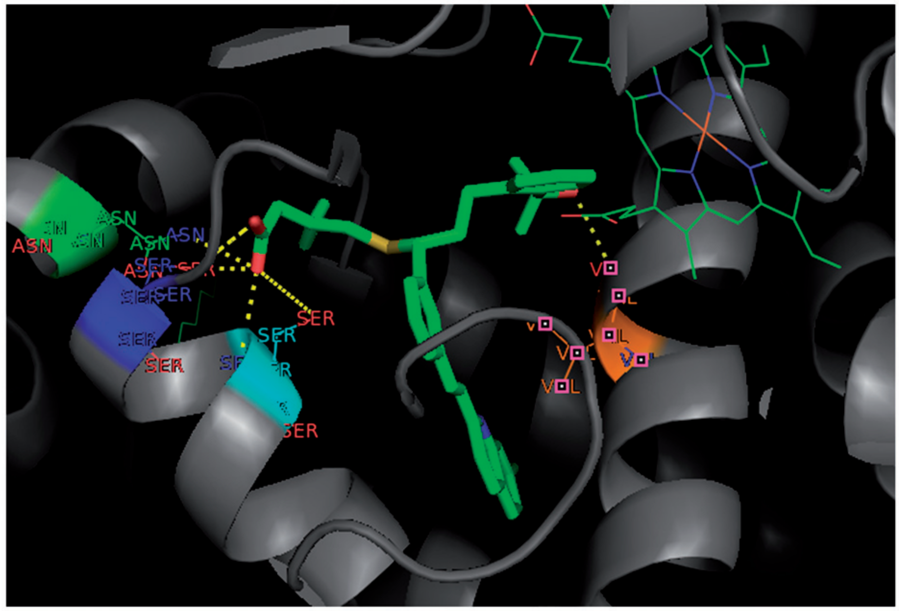

Figure 3. Interaction of montelukast with CYP2C8. Drawn with the software PyMol (DeLano Scientific, Palo Alto, CA) from the atomic coordinates of montelukast CYP2C8 cocrystals (Agarwal et al., 2010), available at the protein data bank.

is being taken in tandem with phenobarbital, phenitoin or rifampin (Buck, 2015).

A report on interaction of montelukast with corticosteroids is also known. A patient taking montelukast and prednisone orally as a treatment for asthma, has gained 13 Kg in weight as the result of a severe peripheral edema, which was resolved upon discontinuation of the corticosteroid while maintaining treatment with montelukast. It is, thus, plausible to infer that montelukast has potentiated the retention of fluids caused by the corticosteroid (Geller, 2000).

The plasma concentration of montelukast may be exceedingly increased upon interaction with drugs that block the main enzyme responsible for its metabolism, CYP2C8. A known inhibitor of CYP2C8 is gemfibrozil (lipid regulating API), which, when co-administered with montelukast, increases its plasma concentration and may lead to rare cases of liver toxicity (Agarwal et al., 2010). Montelukast itself also has good affinity to CYP2C8 (although less than gemfibrozil) and the ability to inhibit CYP2C8. There is, thus, the possibility of interaction of montelukast with other APIs which are metabolized by this enzyme: troglitazone, rosiglitazone and pioglitazone (APIs for the management of diabetes), amodiaquine (anti-inflammatory and antimalarial), amiodarone (antiarrythmic) and cerivastatin (cholesterol-regulating API).

The binding of montelukast to the enzyme CYP2C8 has already been demonstrated *in vitro* (Schoch et al., 2008), as depicted in the Figure 3. The chloroquinoline moiety is docked into a hydrophobic pocket, while the carboxylate group forms hydrogen bonds with serine and asparagine aminoacid residues of the enzyme and the third branch, composed of a tertiary alcohol bound to a phenyl, is positioned close to the heme iron.

New formulations for montelukast

The very limited options available for the delivery of montelukast, along with the higher accessibility to this API which followed the expiry of the patent for Singulair® in 2012 (Merck & Co, 2013) have triggered an increase in the studies aiming at the development of new formulations for this anti-asthmatic medicine. Nowadays we can find a variety of alternative and innovative formulations, which can be classified into three main categories, according to the involved technology:

(I) macroscale formulation uses macromolecules to disperse montelukast, increasing its solubility and embodying it with improved physico-chemical properties and bioavailability;

(II) nano-formulation relies on the incorporation of montelukast into nanoparticles to achieve higher stability and an improved pharmacokinetic profile;

(III) formulations at the molecular level use specific carriers, namely cyclodextrins, which are able to incorporate a molecule of montelukast, or a fragment of its molecule.

Macromolecule-based formulations for improved oral delivery

These new forms of oral delivery are designed to quickly disintegrate, or even dissolve, in the mouth, emerging as attractive alternatives to the conventional formulations. They are particularly useful in pediatric, geriatric and bedridden patients who have difficulty in swallowing (Siddiqui et al., 2011). Furthermore, by making montelukast available for pregastric absorption, in the mouth, pharynx, and esophagus, these formulations help cirvumvent hepatic first-pass metabolism rendering higher the bioavailability.

Orally disintegrating tablets

Orodispersible tablets (ODTs) are designed to disintegrate in the mouth before swallowing. Initially defined as ''a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue'', there is still no consensus on the

maximum disintegrating time. USP's guidelines recommend a maximum of 30 seconds (Center for Drug Evaluation and Research (CDER), 1998), while many other sources cite 1 min as the limit for disintegration. The preparation of ODTs relies mainly on the use of an adequate dispersing agent. These excipients are strongly hydrophilic and receive the common name of 'superdisintegrant' (Figure 4) since they are able to ensure disintegration occurs within a very short period of time.

Successful montelukast formulations as ODTs were reported using as the dispersing agent a cellulose derivative, crosscarmellose sodium (Ac-Di-Sol®) (Chhajed et al., 2012; Sri et al., 2012), modified starch (sodium starch glycolate), the synthetic polymer crospovidone (crosslinked N-vinyl-2-polypirrilidone) or a combination of these (Mahesh et al., 2012; Gupta et al., 2014; Shravani & Rao, 2014; Bhusnure et al., 2015). Some of the reported ODTs were found to require specialized packing and storage conditions (Mahesh et al., 2012), while another set of proposed formulations demonstrated to be stable at $40 \pm 2\,^{\circ}C$ and a relative humidity of $75 \pm 5\%$ for 3 to 6 months (Shravani & Rao, 2014). ODTs comprising an association of montelukast with taste-masked levocetrizine were also reported, with these having a very fast disintegration time of *c.a.* 16 seconds. Stability studies consisted in storing the monteluast/levocetirizine-containing ODTs in aluminum capped clear glass vials for three months at $40 \pm 2\,^{\circ}C$ and a relative humidity of $75 \pm 5\%$ and then measuring monthly their drug content and drug release profile. No significant differences were found ultimately showing that the ODTs are stable over the three months period (Gupta et al., 2014).

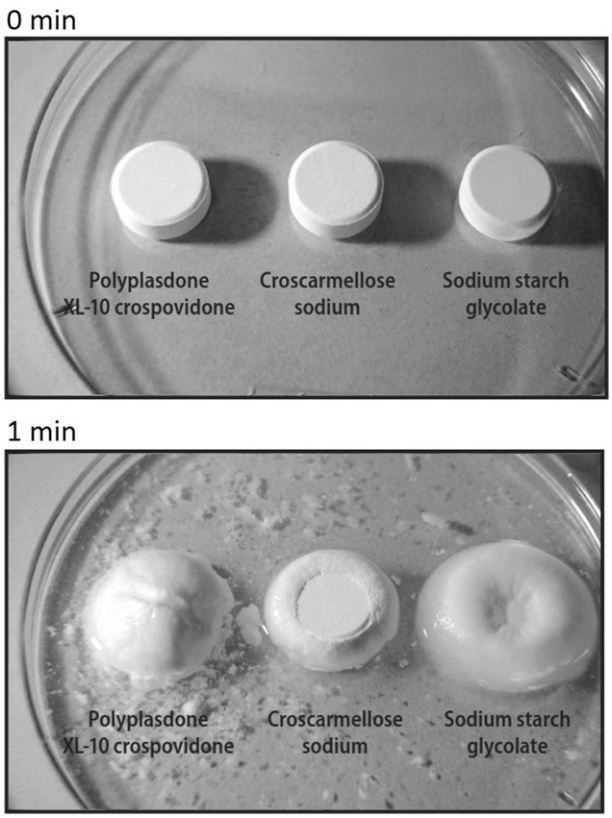

Figure 4. Disintegration, by contact with water, of placebo tablets made with the superdisintegrants crosspovidone (left), crosscarmellose (center) and starch glycolate (right). Adapted from ''Polyplasdone™ crospovidone superdisintegrants product overview'' leaflet, by Ashland Inc.

Fast-dissolving oral films and buccal patches

A trendy alternative to the fast-dissolving tablets are oral thin films which have a more pleasant texture and a good shelf-life. Oral films can be designed to i) dissolve under one minute, being named fast-dissolving oral thin films, or ii) exhibit sustained release mucoadhesive buccal patches. Both formulations favor sublingual absorption, helping to bypass the hepatic first-pass metabolism and increasing bioavailability. Nonetheless, they are sensitive to environmental moisture and require a specialized package which rendered them less affordable and has limited their widespread use (Siddiqui et al., 2011).

Fast-dissolving films of montelukast, dissolving within 30 seconds and having a neutral surface pH, were reported by Ghorwade et al. In their package, these new formulations were demonstrated to be stable at $40 \pm 2\,^{\circ}C$ and at a relative humidity of $75 \pm 5\%$ for 3 months (Ghorwade et al., 2011). Another montelukast fast-dissolving film, developed by Khatoon et al., had a surface pH within 6.35-6.75 (Khatoon et al., 2014). Note that the salivary pH varies from 6.8 to 7.2, which implies that formulations with compatible pH are less prone to cause irritation of the oral mucosa.

Mucoadhesive buccal patches of montelukast allow a sustained release, with 60% to 90% of the API being released within the first 8 hours, as observed by *in vitro* studies (Rao & Suryakar, 2010; Rao et al., 2010; Rao & Suryakar, 2011; Mohamed et al., 2014). A study involving guinea pigs previously sensitized with histamine has demonstrated that the release of montelukast from mucoadhesive patches provides a protective effect against bronchoconstriction for a period of 6 h, whereas when it was administered as solution the protective effect lasted only one and a half hours (Soni et al., 2012a). Further optimization of the mucoadhesive patch was achieved by preparing a bilayer system. Each bilayer patch was loaded with only 5 mg of montelukast (half of the conventional daily dose for adults) since the second layer is designed to protect from leakage in the period of mucoadhesion and permits a unidirectional delivery through the buccal mucosa. In vitro tests have shown a quasi-linear and complete release of montelukast over eight hours (Soni et al., 2012b), but *in vivo* tests are required to prove that bioavailability from these bilayer patches is equivalent to that achieved with conventional tablets.

Encapsulation into nanoparticles

Polymeric nanoparticles for pulmonary delivery

The pulmonary route for drug delivery allows a reduction of the amount of drug administered to the patients, a decrease of the side effects and avoidance of the hepatic first pass metabolism. A handful studies have focused on the development of aerosol forms for the delivery of montelukast, using nanoparticles of chitosan or poly-lactic acid (PLA).

Chitosan [poly (1,4-α-D-glucopyranosamine)] is a bioderived polysaccharide prepared by N-deacetylation of chitin

which has been used in the construction of nanosized drug carriers and gene transfer vectors. Chitosan nanoparticles have been the focus of considerable attention due to their many advantages, including good stability and simple preparation (Agnihotri et al., 2004; Nagpal et al., 2010). In addition, chitosan nanoparticles can facilitate the transposition across cellular barriers and transiently cause opening of the tight junctions between epithelial cells (Hu et al., 2011). The formulation of chitosan nanoparticles for the pulmonary delivery of montelukast allowed its protection from degradation and a sustained release for 24 hours (Inamdar et al., 2013).

A word of caution is, however, required on the use of chitosan nanoparticles. The aforementioned ability to facilitate permeation of epitlhelia means there is the possibility that chitosan nanoparticles will translocate from the gastrointestinal tract, nasal cavity, or alveolar sacs into the systemic circulation (Hu et al., 2011). Toxicity evaluation with 200 nm chitosan nanoparticles on zebrafish embryos has demonstrated signs of physiological and oxidative stress, translating into decreased hatching rates, embryo malformations and dose-dependent increase in mortality rate (Hu et al., 2011).

Poly lactic acid (PLA) is a bio-derived, biocompatible and biodegradable polymer, approved as GRAS by the FDA in the 1970s (Code of Federal Regulations, 2016). It is an excellent material for biomedical applications including sutures, clips, and drug delivery systems (Xiao et al., 2012). Patel et al. produced montelukast-loaded large porous PLA particles and demonstrated that these particles are capable of reducing the inflammation of asthmatic mice, the morphological changes associated with it and the airway hyperreactivity, thus resulting in a more efficient therapy for asthma than the conventional oral dosage forms (Patel et al., 2014).

Lipid nanoparticles with a solid matrix

Lipid nanoparticles are made from physiological lipids, which are both biocompatible and biodegradable, thus having huge advantages over the polymeric nanoparticles that may cause toxic effects as the polymer is degraded *in vivo* (Das & Chaudhury, 2011). Lipids improve bioavailability since they are able to promote oral absorption *via* selective lymphatic uptake. Lipid nanoparticles with a solid matrix have demonstrated to posess a high drug loading (both hydrophilic and lipophilic drugs) and hassle-free large-scale production (Das & Chaudhury, 2011; Patil-Gadhe & Pokharkar, 2014). The small size of the particles, ideally between 120 and 200 nm, helps avoid blood clearance by the reticuloendothelial system (*i.e.*, liver and spleen filtrations are avoided) (Das & Chaudhury, 2011). They are divided into two categories, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).

SLNs were developed in the 1990s, being the first generation of lipid-based nanoparticles. They are not really solid, but they can contain drug crystals, super-cooled mixed phases and crystallised lipids which tend to change to lower energy forms over time (Figure 5). Long-term storage is, thus, difficult because of the risk of instability. Not rarely, the particles burst open and release their load (zur Muhlen et al., 1998; Mehnert & Mader, 2001). Encapsulation of

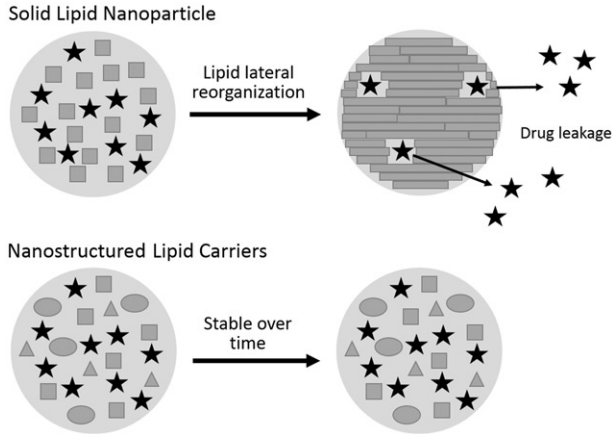

Figure 5. Schematic representation of SLNs and NLCs.

montelukast into SLNs allowed to achieve entrapment efficiencies between 48 and 85%, a variation which depends strongly on the employed lipid. The size range of the SLNs with montelukast lied within the 50 80 nm, and it was demonstrated that these particles were stable in storage for up to 30 days (Priyanka & Sathali, 2012).

NLCs are the second generation of lipid-based nanoparticles. They were developed aiming at addressing the instability and release issues associated with SLNs. NLCs are hybrid nanoparticles blending lipids with very different structures in order to have a matrix 'as imperfect as possible' (which is more stable) (Das & Chaudhury, 2011). Usually, solid lipids and oils are mixed to produce NLCs that are still solid at ambient temperature as well as at body temperature (Müller et al., 2002). NLCs allow a higher loading capacity, with a lower API leakage and they are suitable for incorporation in final dosage forms such as tablets or capsules (Das & Chaudhury, 2011; Patil-Gadhe & Pokharkar, 2014; Weber et al., 2014). Encapsulation of montelukast into NLCs allowed obtaining an entrapment efficiency of 96.1%, corresponding to a montelukast concentration of 2.02 mg/mL. Administration of the montelukast-loaded NLCs to Wistar rats has demonstrated a bioavailability increase of 143 fold (compared to a montelukast aqueous solution), and a sustained release profile over 24 h (Patil-Gadhe & Pokharkar, 2014). The montelukast-loaded NLCs were also tested for pulmonary delivery: controlled and sustained montelukast release was demonstrated *in vitro* by tests on simulated lung fluid (Patil-Gadhe et al., 2014).

Molecular encapsulation with cyclodextrins

Cyclodextrins (CDs), discovered by Villiers when studying the bacterial degradation of starch (Villiers, 1891), are small rings of 1,4-linked α-D-glucose, typically occurring in Nature with six to eight units, being coined α-CD, β-CD and γ-CD. Chemical modification of these native cyclodextrins affords a variety of derivatives with different physico-chemical and biological properties. Of the existing derivatives, now more than 1500 (Nitalikar et al., 2012), the most relevant to pharmaceutical and biomedical applications is 2-hydroxypropyl-β-cyclodextrin (HPβCD), which combines excellent aqueous solubility and solubilizing properties with a good

tolerability *in vivo*, being an FDA-approved excipient for powders, oral liquid and injectable formulations (Food and Drug Administration, nd). Methylated derivatives are also excellent solubilizers and include permethylated β-CD (TRIMEB) and randomly methylated β-cyclodextrins (RAMEB and CRYSMEB, having different number of methyl groups per cyclodextrin unit). TRIMEB, due to its hemolytic action is not suitable for internal use, being used in topical formulations for its ability to enhance drug permeation into cells and across the skin and mucosa. RAMEB is still pending approval for pharmaceutical uses. Other cyclodextrin derivatives that may be used in pharmaceutical applications include 2-hydroxypropyl-γ-cyclodextrin (HPγCD) and sulfobutylether-β-cyclodextrin (SBEβCD), although their high cost still renders them less attractive as excipients.

Cyclodextrins as functional excipients in solid formulations

Cyclodextrins, both native and derivatives, are patented ingredients for the preparation of porous microparticles for the delivery of several APIs, including montelukast. The increased area-to-surface ratio and lower density of these microparticles is claimed to afford higher flowability, suspension rate and bioavailability (Healy et al., 2007).

Cyclodextrins can also be used to help formulate solid particles. In a Chinese patent, HPβCD is used as an excipient in the preparation of solid particles with a combination of two APIs, montelukast and calcium citrate. The product is claimed to have a 'better effect' and to avoid 'damage to vessel wall of the patient' (Chen et al., 2012).

Liquid formulations

Liquid formulations are the preferred administration form for pediatric medicines, particularly in the case of lactants. Liquid formulations for montelukast are, however, currently unavailable in the market, a feature easily understood because of the aforementioned hydrolytical instability, further potentiated by exposure to light. The well-known protective action of CDs against these two damaging agents makes them the perfect approach to circumvent the issue. A handful of studies and patents on the utility of CDs in the preparation of liquid formulations of montelukast are already available. One of these contains native CDs, along with other solubilizers and stabilizers, and claims to have 'superior stability, taste and flavor' (Kwon et al., 2015).

The inclusion of montelukast into chemically modified CDs in aqueous solution was first demonstrated in 2006, using heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) as the host (Duran Meras et al., 2007). Nevertheless, only in 2015 a stable aqueous oral solution of montelukast was achieved, using HPβCD to include the API. The report shows that HPβCD brings a slight increase in the solubility of montelukast sodium and, more importantly, a significant improvement of its stability, with less than 1% degradation and no precipitation occuring after 2 months. Moreover, the oral solution showed similar plasma concentrations and pharmacokinetic parameters to the commercial granules, thus suggesting that it is bioequivalent to them. Concerning storage, it remains physically and chemically stable at 25 °C for at least 12 months (Kim et al., 2015).

HPβCD and/or γ-CD are also claimed to help solubilize and protect montelukast from oxidation in a formula associating it with the antihistamine loratadine. Aiming at nasal delivery, the invention consists of a liquid to semi-solid formulation (gel, suspension or emulsion) (Bhattacharya et al., 2003).

Chronotherapeutic approaches

Resulting from a combination of chronobiology and pharmaceutics, chronopharmaceutics is devoted to the design and evaluation of drug delivery systems that release an API at a rhythm that ideally matches the biological requirement of a given disease therapy. The chronotherapeutic approaches take into account the circadian fluctuations associated with chronic diseases, namely diabetes, arthritis, ulcers and asthma. In asthmatic patients, the airway resistance increases progressively during the night and the lung function reaches a low point in the early morning. A drug delivery system capable of being administrated at night but releasing the drug only in the first hours of the morning is thus a much more effective therapy (Padmaxi et al., 2012; Ranjan et al., 2014). Chronotherapies for asthma are already available with the corticosteroids prednisolone/cortisone (Dutimelan®) (Durrington et al., 2014), theophylline (Uniphyl®) (Leslie, 1986) and the β2 agonists albuterol (Proventil Repetabs®, Volmax®), terbutaline (Bambuterol®) and tulobuterol (Hokunalin Tape®) (Durrington et al., 2014). For montelukast, chronotherepeutic systems under study are currently based on the pulsatile drug release systems. The release occurs in a 'pulse', meaning that the API is released suddenly after a well-defined lag time or time gap, according to circadian rhythm of disease states (Bhutkar et al., 2013). No drug is released from the device within this lag time.

A reservoir system with erodible barrier coating was developed for montelukast, providing a lag time of 5 hours before release. The system consists of press-coated tablets with a coating layer of hydrophylic polymers that swell and erode over the five hours to expose an inner core tablet. These core tablets, containing the superdisintegrant Ac-Di-Sol®, release *in vitro* 70% of the montelukast within 5 mins, followed by the maximum release in 15 mins (Padmaxi et al., 2012). Another proposed system, also based on press-coated tablets, had a shorter lag time, of four hours (Janugade et al., 2009). Besides the tablets, there is also a report on pulsatile release capsules for montelukast, allowing the release of montelukast sodium after 4 hours of administration (Ranjan et al., 2014). These formulations may be helpful for preventing the worsening of asthma occurring in the early morning, from 4 a.m. up to 8 a.m. (Hetzel & Clark, 1980), with proposed administration time around 12 p.m. of the previous day.

Conclusion

This review illustrates how the work performed by various research groups spread throughout the world constitutes a solid foundation to engineer, in the near future, innovative formulations and delivery systems for montelukast, which may bring significant improvements to two main weaknesses: the bioavailability and the instability of this API.

A number of these drug delivery approaches are devoted to the improvement of the bioavailability, based mainly on oral delivery in order to increase pre-gastric absorption and thus avoid loss of drug due to the hepatic-first pass metabolism. This metabolic action is responsible for the reductions of 30 40% of the plasmic concentration of montelukast. The proposed new delivery strategies include orodispersible tablets and fast-dissolving thin films for quick release and onset of action. Nevertheless, the most promising dosage form for absorption in the oral cavity is, in our opinion, the bucoadhesive patches, which were shown to provide a prolonged action, avoiding bronchoconstrition for a period of up to 6 h.

Nanoencapsulation techniques bring a two-in-one solution for montelukast delivery, as they protect it from degradation and simultaneously offer dramatic increases in bioavailability providing that the nanoparticles have the right size to elude liver uptake, that is, between 120 and 200 nm. Montelukast-loaded NLCs proved to be excellent delivery systems in Wistar rats, bringing a 143-fold increase in bioavailability.

Systems designed for local action of montelukast constitute a growing trend in delivery, with PLA nanoparticles being proposed as carriers in the case of pulmonary delivery and cyclodextrins as molecular capsules for the preparation of topic nasal formulations.

A special highlight should be given to the use of cyclodextrins. Literature data is consensual concerning their benefic function towards the aqueous solubility of montelukast, either in the acid or in the salt form, which, in most of the cases, will be enough to lower the amount of drug needed to achieve therapeutically-significant bioavailabilities. Finally, and most importantly, the demonstrated ability of HPβCD to improve the stability of montelukast in aqueous solution to the exposure of light will certainly unlock the door to the development of liquid forms for montelukast, which is of the utmost relevance in pediatry.

Declaration of interest

The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT, Portugal), European Union, QREN, European Fund for Regional Development (FEDER), through the program COMPETE, for general funding to the QOPNA research unit (FCT UID/QUI/00062/2013) and CICECO-Aveiro Institute of Materials, POCI-01-0145-FEDER-007679 (FCT Ref. UID/CTM/50011/2013), financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement.

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