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Formulation approaches for improved retinoids delivery in the treatment of several pathologies

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ABSTRACT

Retinoid acid (RA) and other retinoids are extensively used as therapeutic agents in the treatment of several types of cancer and skin disorders. However, the efficiency of these medical agents is compromised due to the unsatisfactory concentration of retinoids in the target cells/tissues. Furthermore, severe side-effects are related to retinoids administration. Incorporation of retinoids into carrier-based delivery systems using encapsulation technology has been proposed in order to overcome the limitations of using free retinoids in the treatment of several pathologies. The present work starts exploring the competences and the difficulties of using retinoids in health care. The metabolism and the main considerations about the mechanism of action of retinoids are also discussed. The final sections are focused on the most recent studies about RA controlled delivery systems to be used in the medical field.

1. Introduction

Retinoids are a set of bioactive molecules which includes vitamin A (retinol) and its natural and synthetic derivatives. They are signalling molecules involved in reproduction, embryogenesis, cellular proliferation and differentiation, immunological activity, vision and epithelial cellular integrity [1].

Vitamin A was first described in 1913 [2]. It is a fat-soluble vitamin composed of a cyclohexenyl ring, a polyene side chain and a polar end-group (Fig. 1) [3,4].

Vitamin A (retinol), retinal and retinoic acid (RA) are naturally occurring endogenous retinoids (the interconversion between these non-aromatic compounds is described in detail in Section 2) and belong to the first generation of retinoids [4]. RA exists as different isomers and the most common RA isomers include all-trans RA (recognized as the vitamin A metabolite with the highest biological activity [6]), 9-cis RA and 13-cis RA [7] (Fig. 2). The synthetic analogues of these isomers are tretinoin, alitretinoin and isotretinoin, respectively, and they are also included in this group of retinoids [3,8,9]. These compounds are oral and topically administrated. Other synthetic retinoids (RA analogues) were pharmaceutically developed and categorized as retinoids of second (mono-aromatic retinoids), third (polyaromatic retinoids) and fourth (pyranone retinoids) generations [3,10] (Fig. 2). Mono-aromatic retinoids include acitretin and etretinate (orally administrated), while polyaromatic retinoids comprise bexarotene (oral and topically administrated), tazarotene (topically administrated), adapalene (topically administrated) and fenretinide (orally administrated) [3,8,11]. At last, seletinoid G (topically administrated) fits in pyranone retinoids [3].

One of the major focuses of retinoids action is related to its anticancer activity. Retinoids regulate tumor-cell growth through the inhibition of cellular proliferation and induction of differentiation, apoptosis and cellular cycle arrest in pre-cancerous and cancerous cells [5,8,12,13]. Particularly, RA plays an important key role as chemopreventive and/or chemotherapeutic. It is an antitumor agent used to treat acute promyelocytic leukemia (APL) [14], skin [8], lymphoma [9], breast [15], ovarian [16], head and neck [17], cervical [18], lung [19], neuroblastoma [20], glioblastoma [21], glioma [22] and melanoma [23] cancer, among others. In fact, this strategy is the only effective treatment for APL [14]. Food and Drug Administration (FDA) approved the usage of all-trans RA in the treatment of APL since 1995 [24]. However, cancer patients can handle several side-effects due to RA administration. In the treatment of APL many patients became resistant to all-trans RA despite continued treatment [25]. Continuous oral administration or intravenous injection are related to a fast reduction of RA half-life in the blood [26,27]. Accordingly, the brief remissions period observed can be explained through the decrease of concentration of RA in the plasma of patients with cancer [25]. Furthermore, patients treated with all-trans RA may present headache, abdominal pain, nausea and hypertriglyceridemia, among others

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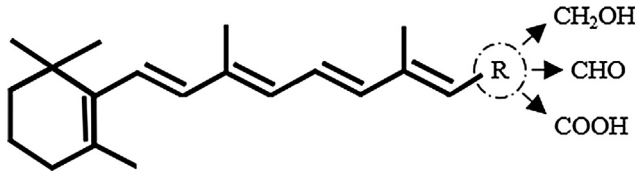

Fig. 1. General structure of retinoids (adapted from [5]). Retinoids with the end groups CH_2OH, CHO and COOH correspond to retinol, retinal and retinoic acid, respectively.

[25,28–30]. Also, patients may suffer of retinoid acute resistance [30], which is characterized by the appearance of fever, dyspnea, pulmonary infiltrates, respiratory distress interstitial, hypotension, pleural and pericardial effusion, high number of white blood cells and acute renal failure [28,31]. Dexamethasone administration can be used to treat this condition [31]. 9-cis RA and 13-cis RA also showed to be effective against some malignancies. 9-cis RA was approved for the cutaneous lesions of Kaposi's sarcoma (topical treatment) [32], while 13-cis RA has been investigated to be used in thyroid cancer treatment [33]. In respect to synthetic retinoids, bexarotene and fenretinide were produced to be used in cutaneous T-cell lymphoma [34] and breast cancer chemoprevention [35], respectively. The development of novel synthetic retinoids was promoted considering the efficiency of natural retinoids, but also as a strategy to decrease the toxicity related to the natural retinoids [11,36].

Retinoids have been also widely used for treatment of some dermatological disorders, namely acne vulgaris, psoriasis and photo damaged skin, among others [37–39]. Herein, tretinoin and isotretinoin are the main compounds to be used in the treatment of acne [8]. Moreover, tretinoin is the most explored retinoid in photoaging therapy [3], as well as seletinoid G [3]. Also, this compound is used to accelerate the skin healing process and to enhance skin appearance [24,40]. At last, it was observed the successful usage of tretinoin in the treatment of pigmentary abnormalities [41,42]. In turn, isotretinoin has been also implemented to treat rosacea, particularly for the subtypes phymatous, granulomatous, steroid-induced rosacea or rosacea fulminans and Morbihan disease [8]. In addition to tretinoin and isotretinoin, adapalene [8] and tazarotene [3] are also used to treat acne. The advantage of adapalene when compared to tretinoin and isotretinoin is the ability to provide higher photostability [8]. The psoriasis treatment have been successfully carried out by the usage of acitretin and etretinate [8] and tazarotene [3]. Most of these retinoids addressed to solve skin problems are topically applied and high doses might be administrated. The side-effects related to this kind of administration include skin irritation (*e.g.* erythema, dryness, peeling, dermatitis and burning at the application site) and high vulnerability to the sunlight which limits retinoids therapy acceptance by patients [8,39,43,44]. These problems are more commonly observed with tretinoin and tazarotene [3]. In turn, the systemic use of retinoids leads to hair loss, conjunctivitis, mucocutaneous xerosis and the increase of transaminases and triglyceride amount [8].

In line with the topics above, retinoids delivery to the patients has been a challenge. In addition to the severe side-effects related to retinoids administration, retinoids may not reach the target cells/tissues in the desired concentrations, which arise as a major constraint for the therapeutic treatment efficiency [45]. It can be explained by the variable retinoid concentration in the plasma (as referred previously), the poor retinoids gastrointestinal absorption and rapid metabolism [46] and the poor solubility in water and highly instability of retinoids in the presence of oxidants, heat and light, among others [1,47]. Accordingly, the routine use of retinoids may not constitute by itself, on its current approach, a competent strategy for the treatment of certain cancers and skin pathologies, as described above. Encapsulation of retinoids into different delivery systems has been explored and projected to improve the conventional methods of administration of these bioactive compounds. The ultimate goal is to increase the bioavailability of these molecules in the human body and, subsequently, become retinoids more efficient as medical agent. Currently, a significant growth in the global encapsulation market is predicted. Particularly, pharmaceutical application dominated the industry, being expected a compound annual growth rate of 11% from 2016 to 2025 [48].

The article provides a general discussion about the metabolism and the mechanisms of action of retinoids and the most recent carrier-based formulations developed for controlled delivery of RA.

2. Retinoids metabolism

The human body cannot produce vitamin A, whereby the practice of a balanced diet is mandatory in order to certify the intake of the recommend supply of this essential nutrient [49]. Dietary sources of vitamin A include carotenoid-rich plants (*i.e.* such as carrots and plants with green leaves [49]) and liver, eggs and milk, which contain retinyl esters, the storage form of retinol [1,4,50]. Among these, the major source of vitamin A is provided in the form of retinyl esters [50]. When ingested and in the first phase of digestion, carotenoids and retinyl esters are dissolved in the food fat phase, forming emulsions in the gastric environment as well as in the duodenum (small intestine) [50]. β-carotene, α-carotene and β-cryptoxanthin might be absorbed by small intestine and taken up by enterocytes. Herein, these molecules are transformed into retinal [51–53]), which is further reduced to retinol. In turn, retinyl esters are first hydrolysed to retinol by pancreatic and intestinal enzymes and then absorbed by the small intestinal lumen [50,54]. Retinol enters the enterocytes and bind to cellular retinol-binding protein type II (CRBP II). It is a specific binding protein with an important key role promoting the re-esterification of retinol with long chain fatty acids through lecithin retinol acyl transferase (LRAT) [53,55]. Nevertheless, a significant amount of retinol remains on its unesterified form, being secreted into portal circulation [56]. The higher amount of formed retinyl esters is afterwards assimilated by chylomicrons which are released from enterocytes to the intestinal lymphatic circulation and then enters into blood circulation [57,58]. The chylomicrons remnants obtained by the hydrolysis of triacylglycerol and the exchange of apolipoprotein in blood circulation [58] are mainly uptake by the liver (hepatocytes) [59], but also by the spleen, skeletal muscle, bone marrow, kidney, adipose tissue, lung, peripheral blood cells and heart for retinol storage on its esterified form [60,61]. In hepatocytes vitamin A can be stored as retinyl esters or retinyl esters can be hydrolysed. Considering the second alternative, the obtained retinol binds to retinol binding protein (RBP), forming the retinol-RBP complex in the hepatocyte [24]. RBP is a hydrophobic protein capable to protect retinol. This step promotes the transference of retinol-RBP from endoplasmic reticulum to the Golgi complex and its further secretion to the plasma of the blood [62]. Moreover, most of unesterified retinol is displaced to the hepatic stellate cells for its storage as retinyl esters [53,59]. In blood, retinol-RBP binds to transthyretin (TTR) to ensure that retinol is uptaken by target cells/tissue. In fact, RBP of retinol-RBP complex is recognized by the trans-membrane protein called stimulated by retinoic acid 6 (STRA6), which is a RBP receptor present in target cells/tissues [24,63–65]. Retinol is internalized and inside the cells this compound can binds to specific CRBP (I and II) or it is reversibly oxidized to retinal (or all-trans retinaldehyde) by retinol dehydrogenase (RDH) [24,66]. Further irreversible oxidation of retinal by retinaldehyde dehydrogenase (RALDH) results in the formation of RA. This isomer can bind to cellular RA-binding protein (CRABP) and be oxidized to 4-hydroxyretinoic acid and 4-oxoretinoic acid by cytochrome P450 enzyme (*i.e.* CYP26) [5,24,66]. This strategy enables to regulate the cellular levels of RA. Instead, RA can enter the nucleus of the cells and bind to specific nuclear receptors and regulate the cellular function considering genomic and non-genomic mechanisms (section 3) [5,24]. An overview about the metabolic interconversion between vitamin A (retinol) natural structures is presented in Fig. 3.

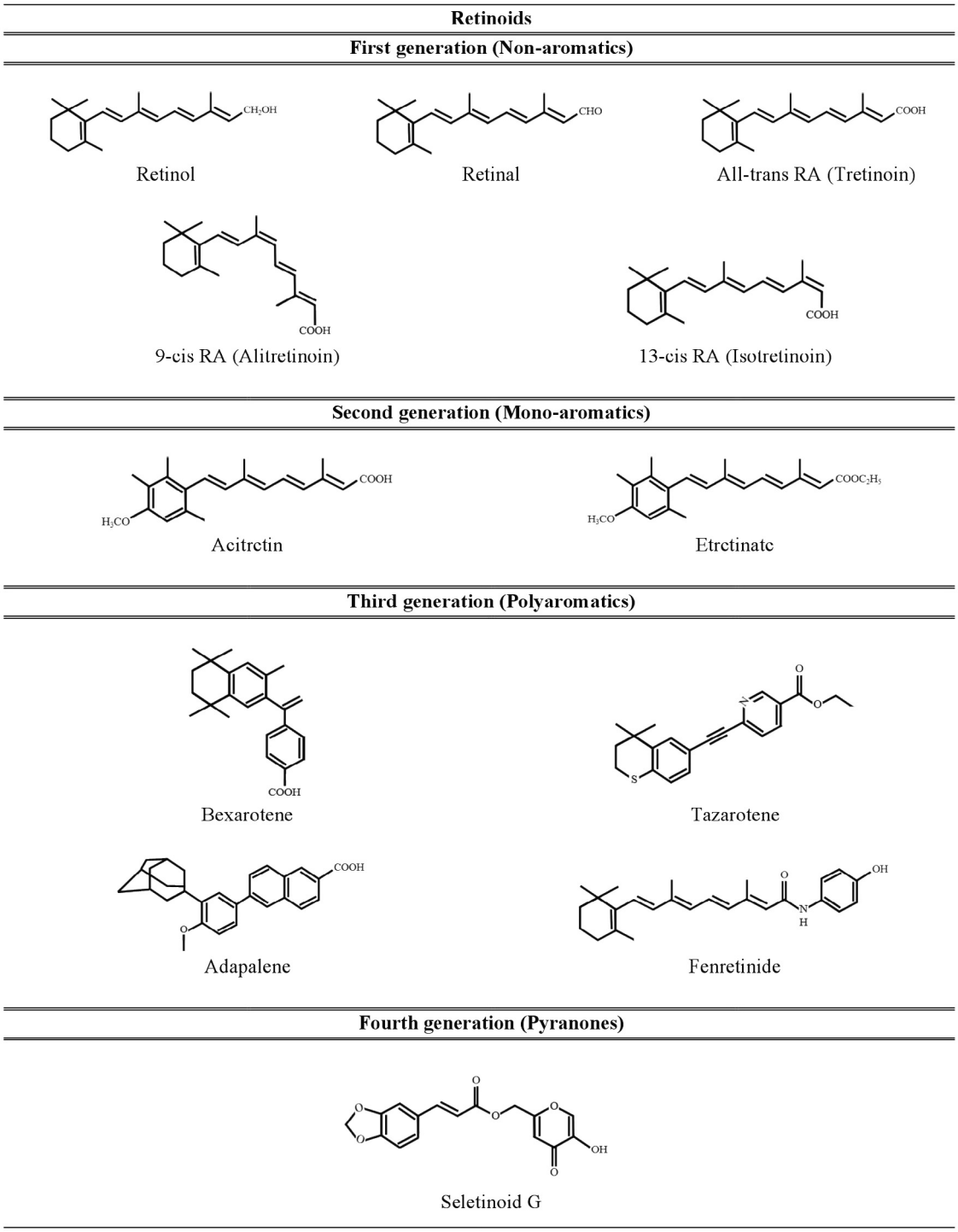

Fig. 2. Retinoids of first, second, third and fourth generation (adapted from [5]).

3. Mechanisms of action of retinoids

Retinoids act by regulating gene transcription mediated through their bind to RA receptors (RARs) and retinoid X receptors (RXRs) [9]. These specific nuclear receptors comprise the most investigated nuclear hormone receptors [68]. Each family of these receptors is associated to three subtypes (*i.e.* RARα, RARβ and RARγ, and RXRα, RXRβ and RXRγ) and each one of them can present several isoforms [5,69]. Accordingly, RARα and RARγ may be present in the isoforms 1 and 2 (RARα1 and RARα2, RARγ1 and RARγ2), while RARβ may arise in the isoforms RARβ1, RARβ2, RARβ3, RARβ4, RARβ5 and RARβ1′. In turn, all subtypes of RXR have the isoforms 1 and 2 (RXRα1 and RXRα2, RXRγ1 and RXRγ2, RXRβ1 and RXRβ2) [70]. Human RARs activation can be carried out by the ligands all-trans RA, 9-cis RA, isotretinoin, etretinate and acitretin, while the ligands for human RXRs only cover 9-cis RA and bexarotene [9].

Retinoids receptors contain five functional domains [5]. Domain A/B is known by encoding the least conserved N-terminal domain, which has an autonomous transcriptional activation function (AF-1). Domain C is highly conserved and it is composed by two zinc finger modules for the binding of DNA. For this reason, domain C is also referred as the DNA-binding domain. Domain D is a hinge which separates the

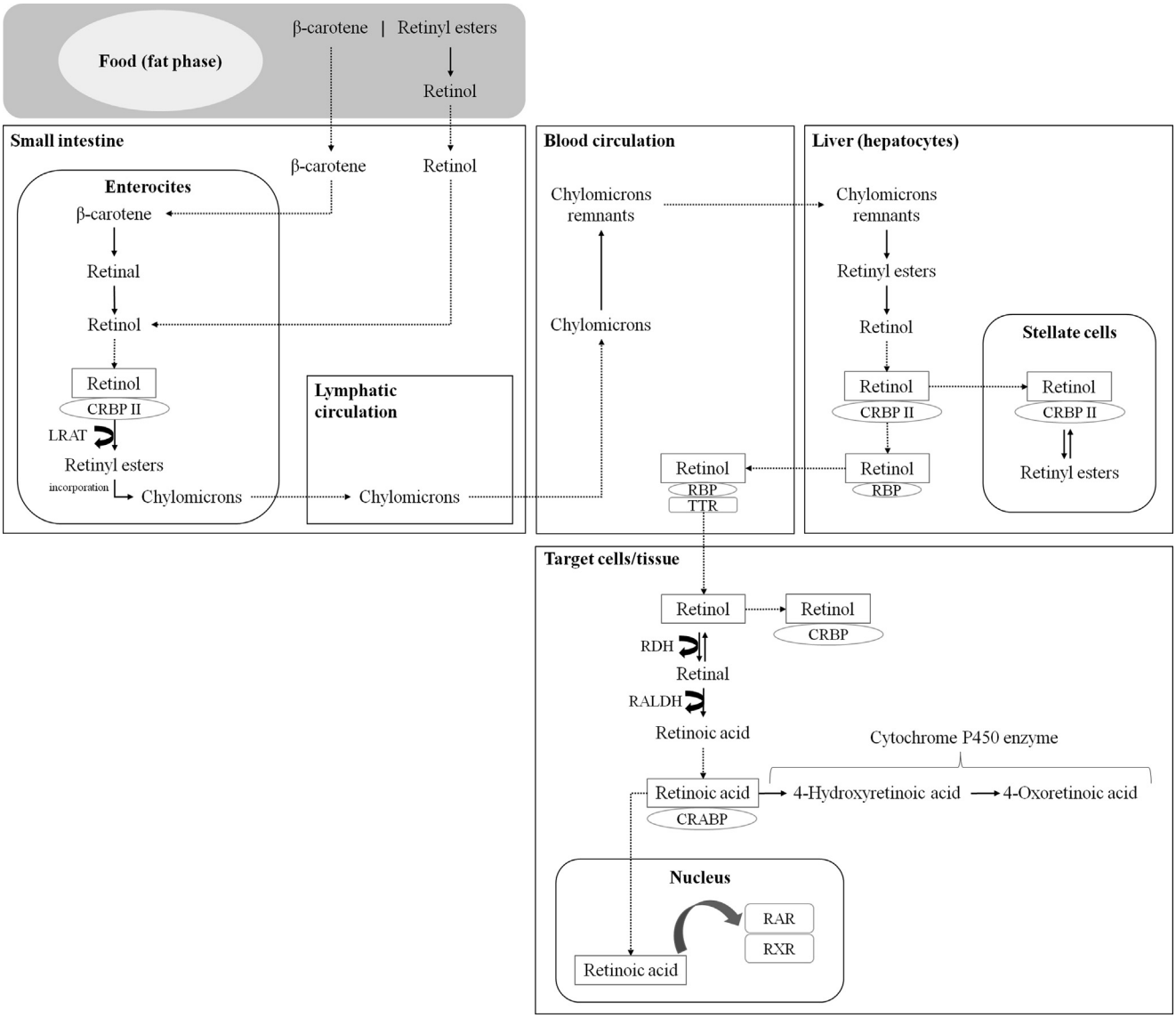

Fig. 3. Metabolic interconversion between vitamin A (retinol) natural structures (adapted from [1,3,10,67]). Abbreviations: CRABP: cellular RA-binding protein; CRBP II: cellular retinol-binding protein type II; LRAT: lecithin retinol acyl transferase; RALDH: retinaldehyde dehydrogenase; RBP: retinol binding protein; RDH: retinol dehydrogenase; TTR: transthyretin; CRBP: cellular retinol-binding protein; RAR: RA receptors; RXR: retinoid X receptors.

domains C and E. Moreover, this domain is involved in the interaction with some nuclear receptor coregulators. Domain E contains the ligand-binding domain and the activation function-2 (AF-2) domain. The ligand binding to the ligand-binding domain promotes a conformational change in the receptor complex and modulates their function. AF-2 is also involved in this conformational change due to an amphipathic α-helix. These conformational changes promote the destabilization of corepressors-binding interface and trigger the recruitment and the interaction with specific co-activators [69]. At last, domain F contains a C-terminal domain which might assist in AF-2 activity.

RXRs can form homodimers (two RXRs) or heterodimers (one RXR and one other receptor) with receptors for vitamin D (vitamin D receptor, VDR), bile acids (farnesoid x receptor, FXR), fatty acids (peroxisomal proliferator activated receptors, PPAR) and RA (RARs), among others [24]. Thus, different signalling pathways can be mediated. Considering the numerous subtypes and isoforms of receptors, it is possible to create a large set of different receptor dimers. Dimerization of receptors is carried out through the interaction of the ligand-binding domain (domain E) of each target receptor [5].

The heterodimer RAR/RXR is crucial for biological activity. It is believed that most of the RA effects are mediated by this receptor dimer [66,69]. In the presence of RAR agonists, their binding to the heterodimer RAR/RXR activates a conformation change and the formation of a ligand-receptor complex. This structure is capable to bind to specific DNA sequences at specific RA response elements (RAREs) and modulate the transcription regulators of several genes and the production of specific target peptides [9,69]. Herein, the enzyme histone acetyl transferase is activated, promoting the chromatin decondensation over the promoter region of target gene. Subsequently, the transcription machinery is activated. It is a process which involves other complexes, namely the thyroid hormone receptor-associated protein [69]. Genes regulated by RA have one type of RAREs that is more frequent to be found (*i.e.* the DR-5 type) and another one that is rare (*i.e.* the DR-2 type) [69]. On the other hand, in the presence of antagonist or in absence of ligands for the RAR/RXR heterodimer, the apo-receptor pair binds to RARE and the corepressor which encodes the activity of histone deacetylase is recruited. The deacetylation of histone is stimulated, occurring the condensation of chromatin and the gene silencing [71].

In addition to the genomic mechanisms, retinoids intermediate non-genomic mechanisms, namely retinoylation (RA acylation). It is a post-

translational alteration of proteins carried out by eukaryotic cells [5].

4. Carrier-based formulations used for controlled delivery of retinoids

Incorporation of retinoids into nano- and/or microparticles has been subject of research in order to improve the performance of these molecules with importance in the pharmaceutical and medical fields. The design of appropriate formulations based on controlled delivery systems has been widely explored to minimize undesirable side-effects due to retinoids administration. Furthermore, this approach might provide an effective protection and stability of retinoids, as well as increase their half-life.

Scientific output reached 81,580 and 12,114 publications related to "encapsulation" and "microencapsulation", respectively. Moreover, 192 publications about "encapsulation" and "retinoic acid" are registered on Scopus database (source: www.scopus.pt, 7th May 2019). The most recent studies (from the last five years) propose several lipid-based carriers for RA encapsulation, including micro-, nano- and emulsions, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), liposomes, niosomes, ethosomes and transethosomes. These types of formulations are recognized to provide a sustained delivery system, in addition to be biocompatible and biodegradable carriers [72]. Furthermore, polymeric carriers such as chitosan, collagen-hyaluronate scaffolds, poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA), poly(ε-caprolactone), hollow mesoporous silica and chitooligosaccharide are also described for incorporation of RA. A brief description about these carriers can be reviewed in the following topic (Section 4.1). Moreover, examples of these retinoids delivery systems are also discussed, highlighting the impact on the bioavailability, bioaccessibility and stability of RA, as well as the therapeutic effect in *in vitro* and *in vivo* studies (Section 4.2).

4.1. Most important methods implemented for RA encapsulation

4.1.1. Emulsions

Emulsions are thermodynamically unstable formulations. They consist of a mixture of two or more immiscible fluids, wherein the liquid of one phase is dispersed as small droplets within the continuous phase [73]. The formation and stabilization of emulsion droplets is achieved by the usage of an appropriate mixture of surfactants and co-surfactants. More simple or complex emulsions can be prepared considering the relative spatial organization of the water and oil phases. Accordingly, water-in-oil (w/o), oil-in-water (o/w), water-in-oil-in-water (w/o/w), water-in-oil-in-oil (w/o/o), oil-in-water-in-oil (o/w/o) and water-in-oil-in-oil-in-water (w/o/o/w) might be produced [74–77]. The droplet size of emulsions can vary between 10 and 100 nm (nanoemulsions), as well as between 100 nm and 1000 μm (conventional emulsions) [78], considering the formulation composition, the homogenization method and operating conditions of homogenizer [78]. Nanoemulsions are transparent and small droplets with more physical stability to gravitational separation, flocculation and coalescence when compared to conventional emulsions [78–81]. In turn, microemulsions can be distinguished from nanoemulsions, since the first ones are thermodynamically favourable formulations despite of the similarity among structures [72].

4.1.2. SLN

SLN are very similar to nanoemulsions, composed of liquid lipids, surfactants and water as previously referred [82]. In case of SLN, the liquid lipids are fully or partly solidified [78,79]. These type of particles are obtained by a controlled crystallization process of the emulsion [83,84], being observed the full crystallization of lipid droplets with the formation of a highly ordered crystalline structure [78].

The main advantages of SNL over nanoemulsions include: (1) the system stability with crystalline lipophilic bioactive compounds (in conventional o/w emulsions the presence of a crystalline lipophilic bioactive compound may cause partial coalescence of the emulsion [85], which might be prevented with the incorporation of the target compound into a lipidic solid matrix), (2) the improvement of lipophilic bioactive compounds stability due to their incorporation into a structured solid matrix and (3) the ability to manage the delivery of the target lipophilic bioactive compound [79]. Moreover, SLN are non-biotoxic carriers, do not require the usage of organic solvents, enable the encapsulation of lipophilic as well as hydrophilic bioactive compounds and their fabrication can be easily scaled-up [86]. The most relevant limitation of using SLN is the high temperatures used during the formation process in order to prevent the crystallization of the lipids [79]. Herein, some heat-sensitive lipophilic compounds may be degraded. Also, the lipids used to form SLN must be highly saturated to ensure the high melting point required to produce the emulsions. This condition implies a damaging effect on human health [79]. Finally, problems related to the low loading capacity, the expulsion of bioactive compounds from particles during storage, the high water content in SLN emulsions and particles aggregation were reported [87–92].

4.1.3. NLC

NLC were developed to overcome the limitations related to the SLN (previously described in Section 4.1.2). NLC are an unstructured solid lipid matrix composed by a mixture of liquid and solid lipids, as well an aqueous phase which contains surfactants and co-surfactants [90,93,94]. The lipidic phase produces a solid matrix with high imperfections in the crystal lattice. Consequently, a higher space is created in the matrix and a higher amount of bioactive compound can be loaded [90,95–97], reducing leakage during storage [98] and preserving the carrier physical stability [94]. In the final, three different types of NLC can be produced, considering the degree of order found in the matrix: imperfect, amorphous and multiple [90].

NLC are suggested as promising pharmaceutical compounds delivery systems due to the usage of GRAS compounds, safety and the availability of large-scalable production methods [94].

4.1.4. Liposomes

Liposome-based systems are the first nano carriers successfully used in clinical applications [99]. Currently, a high number of liposomal formulations has been approved for the cancer treatment. Particularly, the encapsulation of all-trans RA into liposomes is described in clinical trials (phase I/II) - Atragen - to treat advanced renal cell carcinoma by intravenous administration [100]. Furthermore, these products have been also accepted for viral and fungal infections, pain management and photodynamic therapy [99]. An increasing number of liposomal delivery systems are expected due to undergoing clinical trials [99].

Liposomes consist of spherical vesicles with a bilayer of lipids around an aqueous core, whereby hydrophilic and lipophilic bioactive compounds might be herein encapsulated [72,73,101]. They are mainly composed of phospholipids, whose amphiphilic properties favour thermodynamically the formation of liposomes [99,102]. Moreover, sterols (for example, cholesterol) can be incorporated into liposomes for the bilayer stabilization and enhancement of encapsulation and controlled release features [102–105]. Four types of liposome-based systems were developed, namely conventional liposomes, sterically-stabilized liposomes, ligand-targeted liposomes and combination systems [101]. They were proposed to deal with relatively short half-life of liposomes *in vivo*, as well as to improve the retention of the bioactive compounds after *in vivo* administration of liposomes [106].

4.1.5. Niosomes

Niosomes are non-ionic surfactant carriers structurally similar to liposomes, considering the presence of a bilayer [107]. The main constituent of niosomes is cholesterol, although other excipients can be integrated. These carrier-based systems are more stable than liposomes considering the materials involved on their production. Other

Table 1
The most recent RA controlled delivery systems developed for the treatment of several pathologies.

Pathology/Potential application	Administration method	Compound(s)	Carrier-based system/Encapsulation technique	Main results	Reference
Acne	Topical application	Tretinoin and tetracycline	Nanoemulsions and NLC	It was not observed a significant difference in tretinoin skin delivery with the incorporation of tetracycline (*in vitro* studies). The usage of nanoemulsions and NLC improved the antibacterial activity against *Staphylococcus aureus*.	[126]
	Topical application	Tretinoin and lauric acid	SLN	Tretinoin stability was achieved with SNL composed by stearylamine. SLN loaded with tretinoin and lauric acid revealed growth inhibitory activity against *Staphylococcus epidermidis*, *Propionibacterium acnes* and *S. aureus*.	[127]
	Topical application	Benzoyl peroxide and tretinoin	Niosomes	A higher amount of tretinoin and benzoyl peroxide was retained in the skin layers when niosomal gel is used (*in vitro* experiments). Niosomal gel showed to be more effective than antiacne cream (*in vivo* studies): a 4.16-fold lower dose of benzoyl peroxide in niosomal gels provided a similar therapeutic index when compared to the antiacne cream.	[108]
	Topical application	Tretinoin	Microemulsions	Tretinoin microemulsion provides an improved release profile when compared to the one obtained by commercial gels and creams (*in vitro* experiments). A zero order kinetics was observed for tretinoin release profile.	[130]
Psoriasis	Topical application	Tretinoin	Liposomes, ethosomes, SLN and NLC	SLN and NLC increased the skin transport, photostability and anti-psoriatic activity when compared to liposomes, ethosomes and marketed product (*ex vivo* studies).	[128]
Photoaging	Topical application	RA	NLC and PLGA nanoparticles	The UVA exposition promoted RA delivery from NLC and PLGA particles into hair follicles by 4.2- and 4.9-fold, respectively (*in vitro* experiments).	[129]
General skin disorders	Topical application	Tretinoin	Optimized deformable liposomes	Optimum liposomes composed by transcutol increase tretinoin skin penetration when compared to the one obtained for tretinoin cream. This formulation could decrease the side-effects related to conventional tretinoin administration (cream).	[131]
	Topical application	All-trans RA	PVA	A complete release of all-trans RA was achieved in ten days, as well as an increase of tretinoin dermal accumulation in explant pig skin (*in vitro* studies). *In vivo* experiments showed a reduction on the side-effects related to free all-trans RA and the retention of this compound at measurable quantities for up to six days.	[121]
Ovarian cancer	–	All-trans RA	Polymer-oil nanostructured carrier (oil and PLGA)	The formulation proposed is capable to induce apoptotic cell death, as well as to provide higher anti-tumorigenic effects for a long-term in the target cells.	[132]
Lung cancer	–	Tretinoin	Poly(ε-caprolactone)	Tretinoin-loaded lipid-core nanocapsules were capable to deal with the high resistance of human lung adenocarcinoma epithelial cell lines and trigger their apoptosis and cell cycle arrest.	[122]
Prostate cancer	–	RA	SLN	A reduction in cell viability of prostate cancer cells was observed when RA concentration was increased in SLN (9.53% at 200 μg/mL).	[133]
Cancer stem cells	–	All-trans-RA and doxorubicin	Emulsions	Co-delivery of all-trans-RA and doxorubicin might enhance the suppression of tumor growth while reduce the incidence of cancer stem cells.	[134]
Cutaneous melanoma	Topical application	Dacarbazine and tretinoin	Transethosomes and liposomes	Transethosomes contribute for a higher dacarbazine concentration in the plasma (*in vivo* studies). Moreover, this formulation showed higher cytotoxic effect when compared to the other one.	[135]
Gastric cancer	–	Sorafenib and all-trans RA	SLN	Sorafenib/all-trans RA-loaded SLN significantly increase a cytotoxic effect when compared to an individual drug.	[137]
Cancer treatment	–	All-trans RA, doxorubicin and interleukin 2	Lipid-coated biodegradable hollow mesoporous silica nanoparticles	All-trans RA/doxorubicin/interleukin-2 co-loaded dHMLB significantly decreased tumour growth and inhibited metastasis.	[136]
Glioblastoma	–	RA	Chitosan and SLN	Trimethyl chitosan-functionalized RA- loaded SLN increased cell death when compared with the free drug.	[138]
Respiratory tissue regeneration	–	All-trans RA	Collagen-hyaluronate scaffolds	All-trans RA-loaded collagen-hyaluronate scaffolds were capable to increase functional epithelialisation in primary tracheobronchial cells.	[139]
–	Intravenous administration	All-trans RA	Styrene maleic acid copolymer	It was observed RA prolonged blood circulation after intravenous injection of all-trans RA-loaded styrene maleic acid copolymer nanoparticles.	[140]
Cancer treatment	Intravenous administration	All-trans RA and tributyrin	NLC	All-trans RA-tributyrin-loaded NLC were more efficient on inhibition of cell viability comparing to the free drug.	[141]
–	–	All-trans RA and paclitaxel	Chitooligosaccharide	Nanoparticles of chitooligosaccharide could be efficiently taken up by HepG2 cells and transported into the nucleus for all-trans RA and paclitaxel delivery.	[142]

advantages include the osmotic stability and activity of niosomes, their applicability for oral, parenteral and topical administration, their capability to successful delivery of bioactive compounds through the skin using channel-like structures, the ability to improve the stability, oral bioavailability and therapeutic performance of bioactive compound, among others [107,108]. However, it is reported the leaking of bioactive compound from niosomes as well as the hydrolysis of core material which compromises the dispersion shelf life [107].

4.1.6. Ethosomes

Ethosomes differs from liposomes by the presence of high content of ethanol in the vesicles (between 20 and 45%) [109]. They are highlighted by their ability to enhance the skin delivery of several bioactive compounds. In fact, ethosomes enable the bioactive compounds to reach the deep skin layers as well as the systemic circulation [109]. Other advantages regarding this carrier-based system include the low risk profile at a large scale, the high patient compliance due to bioactive compound administration using a gel or a cream and the relative simplicity of ethosomes production [109].

4.1.7. Transethosomes

Transethosomes results from the combination of transferosome (with the ability to become deformable and of skin permeation) and ethosomes [110]. Accordingly, bioactive compound-loaded transethosomes can be absorbed by skin and follow for the systemic circulation. This carrier provides high encapsulation efficiency, protection and a slow controlled delivery of bioactive compounds. Moreover, the preparation process does not require the usage of undue pharmaceutical additives [111–113].

4.1.8. Polymers

Different biodegradable polymers have been used as encapsulating agents to produce carrier-based systems. Due to their biocompatibility and biodegradability, these polymers are widely considered to be applied in medicine [114].

Natural biodegradable polymers present some limitations related to the defective biomechanical characteristics and the complexity of structure. However, they can be chemically modified and be metabolized by the host [115]. Chitosan is a natural biodegradable polymer capable to adhere to the gastric mucosa, does not trigger allergic or irritant reactions, its permeability increases with decrease of pH and the products resulting from its degradation are not toxic [116]. In turn, the natural polymer collagen-hyaluronate scaffolds might arise as a strategy for tracheal regeneration. In a recent study a tracheobronchial epithelial model was developed using a bilayered collagen-hyaluronate scaffold [117]. Collagen-hyaluronate scaffold provides support for growth and differentiation of respiratory epithelial cells. Consequently, a functional barrier is formed which protects and at the same time avoids the proliferation of bacteria [118].

Synthetic biodegradable polymers arise as an alternative to provide a sustained controlled delivery from over several days to weeks when compared to natural biodegradable polymers. However, they can be involved in toxicity problems and chronic inflammation [119]. PLGA was approved by US FDA and European Medicine Agency to be used in controlled delivery formulations, being one of the most used biodegradable polymers [120]. PVA is reported as safe *in vivo* in addition to present mucoadhesive nature, which is an advantage increasing the residence time of target bioactive compounds within tissues [121]. Poly (ε-caprolactone) is referred as a biodegradable polymer [122]. Hollow mesoporous silica enables the production of nanoparticles with an extensive central hole and an external mesoporous silica shell. The advantages about this type of particles include the large surface area, the ability to control the pore diameter, low density, stability, high loading capacity and the possibility to encapsulate and storage bioactive compounds with volatile properties [123]. Styrene maleic acid is a low-cost copolymer with good durability, non-toxic and no teratogenic effects [124]. Chitooligosaccharide is a depolymerization product of chitosan. It displays antibacterial and antitumor activities, as well as improves immune activity [125].

4.2. RA controlled delivery systems for therapeutic applications

Recent studies (from last five years) have reported feasible RA carrier-based formulations to be used to treat acne, photoaging, psoriatic and several types of cancer (Table 1). As far as acne therapy is concerned, Lin et al. [126] investigated the usage of two different carrier-based systems – nanoemulsions and NLC – to incorporate a combination of tretinoin and tetracycline to treat this disease. This research reported, for the first time, the impact of encapsulating simultaneously two drugs on the skin permeation and on the antibacterial activity against microorganisms involved in acne (*in vitro* studies). The obtained results evidenced that tretinoin permeation was mostly unchanged after this drug encapsulation, being enhanced the tretinoin delivery via follicular routes when NLC were used. Moreover, the incorporation of tetracycline did not incite a significant difference in tretinoin skin delivery. However, tetracycline permeation decreased by 2-fold. In terms of the antibacterial activity, it generally was not affected by the usage of a dual-drug system. The usage of nanoemulsions and NLC only improved the antibacterial activity against *Staphylococcus aureus*. Later, Silva et al. [127] combined tretinoin and the antimicrobial lauric acid in SLN as a new strategy for the topical acne treatment. In the study, SNL with and without stearylamine were produced. Retinoid stability was only obtained with SNL composed by stearylamine. Also, SLN loaded with tretinoin and lauric acid showed to be efficient on inhibiting the growth of *Staphylococcus epidermidis*, *Propionibacterium acnes* and *S. aureus* (*in vitro* studies). Gupta et al. [108] suggested another carrier-based system to be used in the treatment of acne. They proposed the encapsulation of tretinoin and benzoyl peroxide (a powerful antibacterial) into niosomes. *In vitro* experiments revealed that a higher amount of tretinoin and benzoyl peroxide is retained in the skin layers when niosomal gel is used instead of a cream and an alcoholic solution. On the other hand, *in vivo* studies showed that niosomal gel is more effective than the antiacne cream, since a 4.16-fold lower dose of benzoyl peroxide in niosomal gel provide the similar therapeutic index of the antiacne cream.

Considering psoriasis disease, Raza et al. [128] developed tretinoin loaded lipid-based carriers – SLN, NLC, liposomes, ethosomes – for improvement of photostability, pharmacodynamic efficacy and skin delivery of this retinoid. *Ex vivo* experiments were performed using bioadhesive hydrogels of the above formulations. Herein, porcine skin (for skin permeation and skin retention analysis) and mouse tail model (for the evaluation of anti-psoriatic activity) were used. The obtained results showed that SLN and NLC provide higher skin transport, photostability and anti-psoriatic activity when compared to liposomes and ethosomes, and even to the marketed product.

Photoaging is referred as the responsible for damage of skin-barrier function. Accordingly, Hung et al. [129] examinated the effect of ultraviolet irradiation on the cutaneous penetration of NLC and PLGA polymer nanoparticles loaded with RA (*in vitro studies*). Broadly, UVA exposition increased the RA delivery from NLC and PLGA particles into hair follicles by 4.2- and 4.9-fold, respectively. The *in vivo* skin distribution of particles was also analysed using nude mouse skin.

Other studies were performed, focusing on development and optimization of potential carrier-based formulations for dermal drug delivery. For instance, Mortazavi et al. [130] proposed microemulsions for tretinoin encapsulation considering the acne treatment. The optimized microemulsions were composed of 15% olive oil, 12% propylene glycol (the co-surfactant), 33% Tween® 80 and 40% distilled water. *In vitro* release experiments revealed that tretinoin microemulsion provides an improved release profile when compared to the one obtained by the commercial gels and creams. Moreover, a zero-order kinetics was observed for tretinoin release profile. Bavarsad et al. [131] projected

the development and optimization of deformable liposomes for topical delivery of tretinoin. For optimum liposome formulations, the presence of transcutol in the liposomes composition resulted in a higher tretinoin skin penetration when compared to the one obtained for tretinoin cream. Also, this strategy could decrease the side-effects related to conventional tretinoin administration (cream). Castleberry et al. [121] encapsulated all-trans RA by their covalently bonding to PVA using a hydrolytically degradable ester linkage. A complete all-trans RA release was achieved in ten days, considering *in vitro* experiments. Moreover, an increase of drug dermal accumulation in explant pig skin was observed. In turn, *in vivo* tests demonstrated a reduction on the side-effects of free all-trans RA (local inflammation), in addition to retain this molecule at the application site at measurable quantities for up to six days.

Design and development of new retinoid-based encapsulation systems to treat cancer have been gathered some new studies. Narvekar et al. [132] evaluated the therapeutic effect of encapsulated all-trans RA against ovarian cancer. A polymer-oil nanostructured carrier with PLGA was used. This formulation was capable to extensively induce apoptosis and provide higher anti-tumorigenic effects for a long-term in the ovarian cancer cell subline SKOV-3_{PR}. Furthermore, Schultze et al. [122] reported, for the first time, the ability of tretinoin-loaded lipid-core nanocapsules (prepared by interfacial deposition of poly(ε-caprolactone)) to solve the huge resistance of human lung adenocarcinoma epithelial cell lines (A549) to the anticancer activity of free tretinoin. Accordingly, apoptosis and cell cycle arrest were induced. Akanda et al. [133] researched the anticancer efficiency of RA loaded SLN over prostate cancer cells. A reduction in viability of these cells was observed when RA concentration was increased in SLN (9.53% at 200 μg/mL). Sun et al. [134] simultaneously encapsulated into a single emulsion all-trans RA and the chemotherapy agent doxorubicin. The final aim was to enable the co-delivery of these compounds and, therefore, provide an efficient strategy for destruction of malignant cells. This approach enhanced the suppression of tumour growth at the same time decreased the incidence of cancer stem cells, considering a synergistic manner. Following the same strategy of Akanda et al., Lei et al. [135] proposed the dual drug encapsulation (in this case, dacarbazine and tretinoin) into transethosomes and liposomes for the treatment of cutaneous melanoma. *In vivo* studies showed that transethosomes contribute for a higher dacarbazine concentration in the plasma. Also, transethosomes showed higher cytotoxic effect when compared to the other formulations. Kong et al. [136] constructed lipid-coated biodegradable hollow mesoporous silica nanoparticles for co-encapsulation of all-trans RA, doxorubicin and interleukin 2. This proposed formulation significantly decreased tumour growth and inhibited metastasis. Li et al. [137] was capable to significantly increase a cytotoxic effect when sorafenib/all-trans RA were both incorporated into SLN. Also, the combination of miRNA coupled with this formulation might be used in gastric cancer treatment. Liu et al. [138] prepared trimethyl chitosan-functionalized RA-loaded SLN to improve the effective treatment of glioblastoma. This carrier-based system increased cell death when compared with the free drug. O'Leary et al. [139] developed all-trans RA-loaded collagen-hyaluronate scaffolds capable to increase functional epithelialisation in primary tracheobronchial cells. Yamamoto et al. [140] prolonged RA in blood circulation when all-trans RA-loaded styrene maleic acid copolymer nanoparticles were injected via intravenous. Silva et al. [141] concluded about the importance of including tributyrin into all-trans RA loaded NLC, in order to increase the encapsulation efficiency. Also, tributyrin- all-trans RA loaded NLC exhibited higher inhibition of cell viability when compared to the free drug. At last, Zhang et al. [142] presented chitooligosaccharide as promising nanoparticles for co-delivery of all-trans-RA and paclitaxel.

5. Concluding remarks

The requirement of retinoids in health care forced the creation of strategies to maximize retinoids efficiency. In fact, current administration of retinoids is a challenge not only because the insufficient retinoid concentration which reaches the target cells/tissues (responsible for the brief remission observed in APL patients), but also by the several side-effects reported. Encapsulation technology seems to provide the protection and stability required for retinoids. Moreover, this strategy might beneficiate these compounds in controlled release studies. Accordingly, it is expected to increase the bioavailabity of retinoids in the human body and thus increase retinoids efficiency. The ongoing investigation on encapsulation of retinoids counts with numerous studies which propose properly carrier-based formulations for retinoids application in the pharmaceutical and medical fields. However, the total number of retinoid-controlled delivery systems in clinical trials is still limited, whereby it is important to insist in this investigation topic.

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