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Review Article

Diosmin in therapy: challenges in clinical application and potential of drug delivery approaches – A review of literature and patents

Cinzia Cimino [a,b,c,*], Angela Bonaccorso [a,b,c], Teresa Musumeci [a,b,c], Claudia Carbone [a,b,c], Rosario Pignatello [a,b,c]

[a] Laboratory of Drug Delivery Technology, Department of Drug and Health Sciences, University of Catania, Catania, 95125, Italy
[b] NANOMED, Research Centre for Nanomedicine and Pharmaceutical Nanotechnology, University of Catania, Catania, Italy
[c] CERNUT, Research Centre on Nutraceuticals and Health Products, University of Catania, Catania, Italy

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ABSTRACT

In recent years, scientific research has shown growing interest in the therapeutical applications of diosmin, as demonstrated by the number of related publications. In fact, this compound possesses numerous properties: cardiovascular, neuro-, retinal, liver and renal protection, and anti-diabetes, anticancer, anti-inflammatory, antimicrobial and antioxidative activities. Nevertheless, its therapeutical application is limited by its molecular characteristics that hinder bioavailability. Based on these considerations, this review aims to explore the advantages and limitations of diosmin therapy, underlining the significance of employing drug delivery systems for its administration. After an overview regarding the commercially available pharmaceutical forms containing diosmin, a comprehensive review of the literature was conducted, and the developed carriers were reported and illustrated, belonging to various classes: polymeric nanoparticles, nanocrystals and nanosuspensions, nanofibers and scaffolds, nanogel and hydrogels, lipid-based nanocarriers, cyclodextrin-based systems, metal nanoparticles, protein-based nanocarriers. These carriers developed to deliver diosmin are herein described focusing mainly on the technological characteristics of the platforms, while also highlighting the potential advantages in enhancing diosmin bioavailability through *in vitro* and *in vivo* evidence. The analysis of literature studies, categorized by route of administration, allows the reader to correlate the characteristics of the carrier with the nature of the biological barrier encountered after the administration, providing insights on the potential use of various types of DDS for different routes of administration and for the treatment of several diseases. In the interest of completeness, the few existing published patents concerning the drug delivery platforms for diosmin administration are also presented. In conclusion, the final section on current challenges and future perspectives highlights the need for further research in this area in order to fill the existing gap in scientific knowledge.

1. Introduction

Diosmin belongs to the flavonoid class, being a natural polyphenolic compound, converted from hesperidin through a dehydrogenation process [1]. It could be extracted from the pericarps of citrus fruits, such as *Citrus reticulata* and from some other medicinal herbs [1], [2]. It was firstly identified in *Scrophularia nodosa* and was recognized as a therapeutic agent in 1969 [3], [4].

In order to explore the pharmaceutical forms currently approved for diosmin administration in Europe, a search among the official databases of the 29 European members was conducted, since the European Medicine Agency (EMA) website directs to the databases of each individual country. The collected data are displayed in the histogram in Fig. 1, for a total of 357 approved products. As it emerges, the main administration route is the oral one, with the 98.9% of the total European commercialized products; among them, coated tablets represent the 79.0% of the total, non-coated tablets are the 17.4%, while other oral pharmaceutical forms account for the 2.5% (splitable tablets, capsules, granules, oral powders, oral suspensions). The remaining 1.1% of the European approved diosmin products consists of formulations designed for topical application, in particular cremes and ointments. The distribution of commercialized dosage forms reflects the primary purpose for which diosmin is marketed, which is the cardiovascular protection in the treatment of chronic venous pathologies.

* Corresponding author. Department of Drug and Health Sciences, University of Catania, Via Valdisavoia 5, 95123, Catania, Italy.
E-mail address: cinzia.cimino@unict.it (C. Cimino).

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However, diosmin possesses numerous other therapeutic properties, which will be outlined below aiming to suggest a broader range of clinical applications. On the other hand, its molecular structure poses several challenges regarding its bioavailability, thus its structure will therefore be analyzed in order to investigate the issue of its low bioavailability after oral or topical administration.

In this context, the aim of this work is to present the multiple therapeutic potentials of diosmin, including for the first time -to the best of our knowledge-a specific focus on drug delivery systems. With regard to the traditional pharmaceutical forms currently on the market, a state-of-the-art review, complemented by currently published patents, will provide a comprehensive overview of the situation and offer insights for filling the gaps currently present in the market.

1.1. Therapeutic activity

Diosmin possesses several therapeutic activities, which are illustrated in Fig. 2 and briefly summarized below; more detailed information can be found elsewhere [1], [2], [4], [5].

Cardiovascular protection [4], [5] is the main therapeutic activity for which diosmin is currently commercialized: its ability to downregulate the expression of mediators, such as tumor necrosis factor (TNF-α), interleukin 6 (IL-6), vascular endothelial growth factor C (VEGF-C), vascular endothelial growth factor A (VEGF-A), and fibroblast growth factor 2 (FGF2), results in the reduction of angiogenesis and inflammation in chronic venous pathologies. Moreover, it appears to possess anti-platelet/anti-thrombotic properties, which was studied *in vivo* in a rat model and is likely associated to enhancement of heparin binding. Furthermore, diosmin has anti-hypertensive effects related to its anti-oxidative and anti-inflammatory properties, which result in the amelioration of cardiovascular complications of metabolic syndrome and in the prevention of cardiac functioning alterations. Finally, diosmin could be helpful in preventing myocardial infarctions, hyaline arteriopathy, and fibrinoid necrosis, thanks to a combination of several therapeutic pathways.

The antidiabetic activity [2], [5] is related to the improvement of some parameters as glycemia, dyslipidemia and glycoproteins profiles, but also to the ability of reducing diabetic neuropathic pain. The mediators regulated by diosmin are: hexokinase, glucose-6-phosphate dehydrogenase, superoxide dismutase (SOD), nuclear factor-kappa B (NF-κB), cyclic guanosine monophosphate (cGMP), protein kinase G, interleukins (IL-1β and IL-33/St2).

The induction of senescence, autophagy and apoptosis is responsible of diosmin anticancer activity, and it involves several mediators, as p53, protein kinases, metalloproteinases, caspases, etc. [2], [5].

The anti-inflammatory activity is obtained through the reduction of several pro-inflammatory compounds, such as cytokines (interleukins IL-2, IL-6, IL-17, TNF-α), cyclooxygenase (COX-2), inducible nitric oxide synthase (iNOS), NF-κB [2], [5].

The anti-microbial activity is mainly achieved through the inhibition of various enzymes; moreover, diosmin could inhibit the transduction, and could promote the alteration of cell membrane permeability [5].

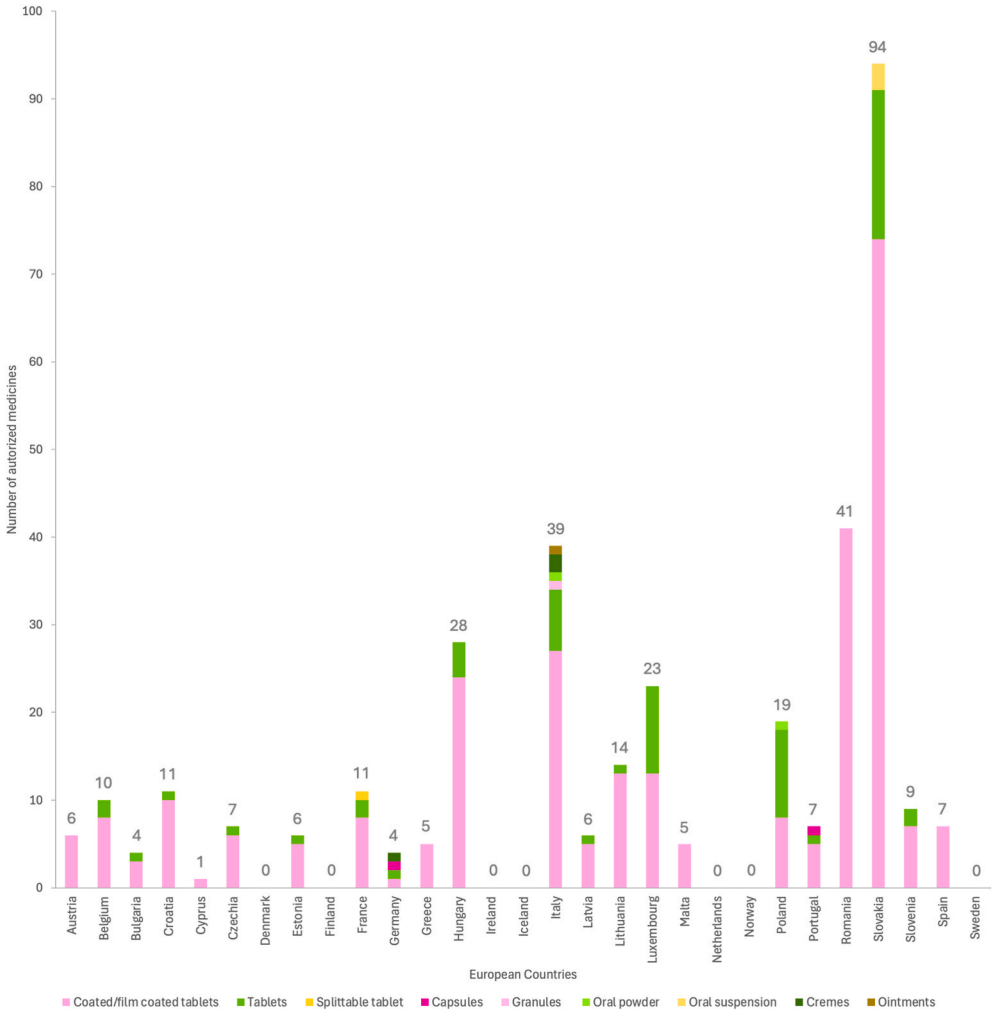

Fig. 1. Number of authorized medicines containing diosmin, classified per European country, with details of the pharmaceutical forms (last updated on 20.03.2026).

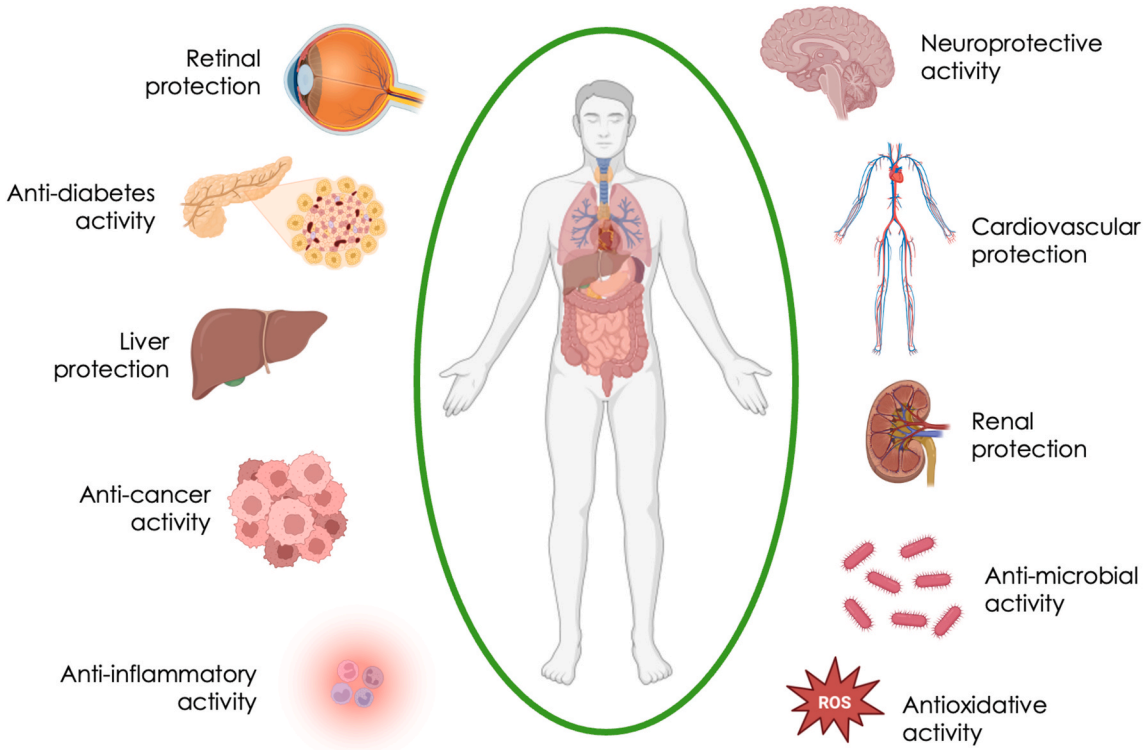

Fig. 2. Diosmin therapeutic activity.

Antioxidant activity is related to the ability to normalize both enzymatic and non-enzymatic antioxidant levels as well as the products of the lipid peroxidation; some of the mediators involved are SOD, catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST), iNOS [2], [5].

The retinal protection is useful in ischemia/reperfusion injury through the reduction of capillary permeability and the maintaining of the integrity of the tight junctions; moreover, the diabetic retinopathy could be ameliorated due to diosmin ability to inhibit aldose reductase (AR), while vision impairment is reduced through the downregulation of c-Jun N-Terminal Kinase (JNK) and p38 mitogen-activated protein kinases (p38-MAPK) phosphorylation [4].

Neuroprotective activity of diosmin was reported for hyperalgesia, neuropathic pain, diabetic neuronal affections, amyloid related pathologies, cognitive impairment and traumatic brain injury; it is related to the ability of modulating NO/cGMP/PKG/KATP pathway, antagonizing the transient receptor potential vanilloid 1 (TRPV1) receptor, reducing hen egg white lysozyme (HEWL) aggregation, reducing the expression of TNF cytokine, and inhibiting acetylcholinesterase (AChE) enzyme [4], [5]. Moreover, diosmin seems to exert a sedative action without modulating the $GABA_A$ receptor [4], [6].

The liver protection ability of diosmin is related to the modulation of Kelch-like ECH-associated protein 1 (Keap-1) and Nuclear Factor Erythroid 2-related factor 2 (NRF2), and also p38 MAPK/NF-κB/iNOS pathways. This property was demonstrated *in vivo* for hepatopulmonary syndrome, liver cirrhosis, hepatic ischemia/reperfusion and alcohol-induced hepatotoxicity [4], [5].

Renal protection is exerted through the reduction of blood glucose and plasma insulin, as well as through the downregulation of NF-κB, and demonstrated to be useful in diabetic nephropathy, acute kidney injury, nephrolithiasis and renal disfunctions [4].

1.2. Physicochemical and molecular characteristics

Diosmin chemical structure is represented in Fig. 3. It is well known that some physicochemical and molecular characteristics could limit drugs bioavailability; for this purpose, in Table 1 are reported the values of some relevant physicochemical and molecular properties [7] that could influence diosmin bioavailability after oral and topical administration.

The analysis of the physicochemical and molecular properties of drugs and of their influence in determining bioavailability after oral administration were deeply studied about thirty years ago and resulted in the so-called “rule of 5” developed by Lipinski and colleagues in 1997 [8]. This theory states that if some parameters are higher than a certain value, that molecule will probably possess poor bioavailability after oral administration. In details, the permeation/absorption of a molecule decreases when its molecular weight (MW) is higher than 500, its logP is higher than 5, it has more than 5 hydrogen bond donors and 10 hydrogen bond acceptors [9]. The only parameter that seems to be adequate for diosmin oral absorption is the logP, while all the other mentioned properties seem to be unfavorable. Some years later, in 2002, Veber and coworker found out that polar surface area and molecular flexibility are more relevant than the MW itself, but with consistent results: an increased rigidity by reducing rotatable bonds causes increased oral bioavailability, while an increased polar surface area generates the opposite effect [10]. Despite passive diffusion is not enantioselective, chirality could have an influence in oral bioavailability if the transport is mediated by carriers or if some excipient of the formulation is chiral, thus this could impair drug release [9]; having 10 stereocenter, this aspect should be taken into account for diosmin oral absorption.

Dissolution of the drug into gastrointestinal fluids is a key element in oral bioavailability, and it is related to solubility; the latter, together with permeability, determines the Biopharmaceutics Classification System (BCS) of the Food and Drug Administration (FDA) [11]. Solubility is related to the logP and to the solvation energy, necessary to overcome hydrogen bonds and interact with water; it is also related to the melting point, as the energy required to disassemble the crystalline structure before dissolution [9]. Finally, solubility is also related to pH ionization and dissociation constant pKa, in particular relating to the acidic gastric environment which could cause precipitation of insoluble

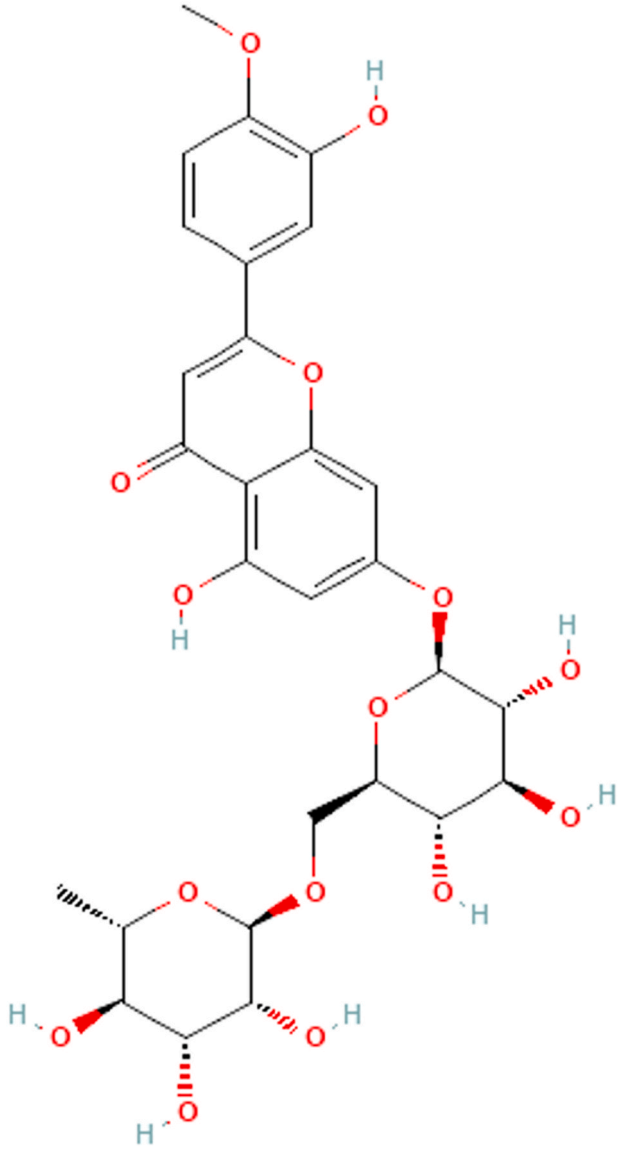

Fig. 3. Diosmin structure [7].

Table 1
Diosmin physicochemical and molecular properties [7].

Parameter	Value
Molecular weight	608.5 g/mol
Hydrogen bond donor count	8
Hydrogen bond acceptor count	15
Rotatable bond count	7
Topological polar surface area	234 Å^2
Atom stereocenter count	10
Covalently bonded unit count	1
Boiling point	926.8 ± 65.0 °C
Melting point	277-278 °C
Solubility	0.019 ± 0.005 mg/L
LogP	2.05
Dissociation constant pKa	6.10 ± 0.40

salt of basic compounds, while the opposite effect could occur in intestine [9]. According to the United States Pharmacopoeia, a drug is considered hydrophilic if its solubility in aqueous medium is higher than 33 mg/ml [12] ; thus, basing on this affirmation, diosmin characteristics could jeopardize its oral bioavailability, belonging to the BCS class IV (low solubility and low permeability) [13].

Permeation after dermal administration is also greatly influenced by drug features. The molar mass of the drug should be lower than 500 g/mol or the molecular weight should be lower than 400-500 Da [14], even if molecules with greater MW could penetrate the skin by disorganizing the cell structure [15]. Considering the diosmin characteristics, this aspect should be taken into account.

Permeation is also affected by logP and polarity; in fact, lipophilic drugs could remain entrapped in the stratum corneum, while hydrophilic molecules could be prevented to overcome the sebum layer [15]. Basing on these statements, diosmin logP value seems to be appropriated since it falls within the moderate range (between 1 and 5) [16]. pH of the carrier and pKa of the molecule could also influence the transport across the skin, thus should be evaluated [15]. Other factors to be evaluated should be the potency (< 10 mg/day) and the melting point (< 250 °C) [16].

2. Diosmin and drug delivery systems in literature

The advantages of encapsulation of hydrophilic molecules into drug delivery systems (DDS) are well-known: amelioration of drug pharmacokinetic, protection from degradation, targeted delivery and controlled release, reduction of side effects [12]. For these reasons, the employment of DDS could result in higher patient compliance, increased safety, and enhanced efficacy [17].

The interest in diosmin application is growing, as demonstrated by the number of publications in PubMed database ([18] last updated on last updated on 01.04.2026) using the keyword “diosmin” (Fig. 4).

Currently, only few research papers are available in literature regarding the encapsulation of diosmin into DDS (mainly starting from 2018), but they are very diversified in terms of types of developed platforms. The search performed using the keywords “diosmin delivery” returned 11 results but some of the papers did not include delivery systems, while the keywords “diosmin nanoparticles” returned 17 results almost all relevant. Other used keywords (“diosmin liposomes”, “diosmin niosomes”, “diosmin hydrogel”, “diosmin carrier”, “diosmin vesicles”, “diosmin emulsion”, “diosmin nanoemulsion”, “diosmin microemulsion”, “diosmin cyclodextrin”) returned redundant references and just a couple more publications compared to the former research.

Herein, a summary of the platforms developed for the delivery of diosmin – divided by type – is graphically reported in Fig. 5. As emerges, a plethora of DDS were developed, with various characteristics, and, more importantly, aimed at many pathologies via different administration routes.

In the following paragraphs, a comprehensive analysis of these research works is proposed, focusing on the technological characteristics of the platforms that are reported in tables; detailed information about characterization techniques could be found in dedicated review [19], [20]. If examined, the *in vitro* or *in vivo* evidence of the increased diosmin activity after encapsulation are reported and commented in the text of the following sections. Literature studies are reported according to the route of administration.

2.1. Oral administration

As deeply discussed, oral administration of diosmin is the most common administration route, for its high patient compliance. The absorption of a compound administered by oral route occurs after being subjected to dissolution, and in particular firstly the disintegration in the stomach and subsequently the dispersion and the dissolution in the gastrointestinal tract, which is followed by the drug permeation [21]. Oral absorption is thus influenced by variables relating to patients’ physiological and pathological conditions, such as pH of the gastric fluid, water volume in the gastrointestinal tract, time of gastric emptying and time of intestinal transit, presence of food in the gastrointestinal tract (detailed insights could be found elsewhere [21]). In addition, also drug physicochemical and molecular characteristics

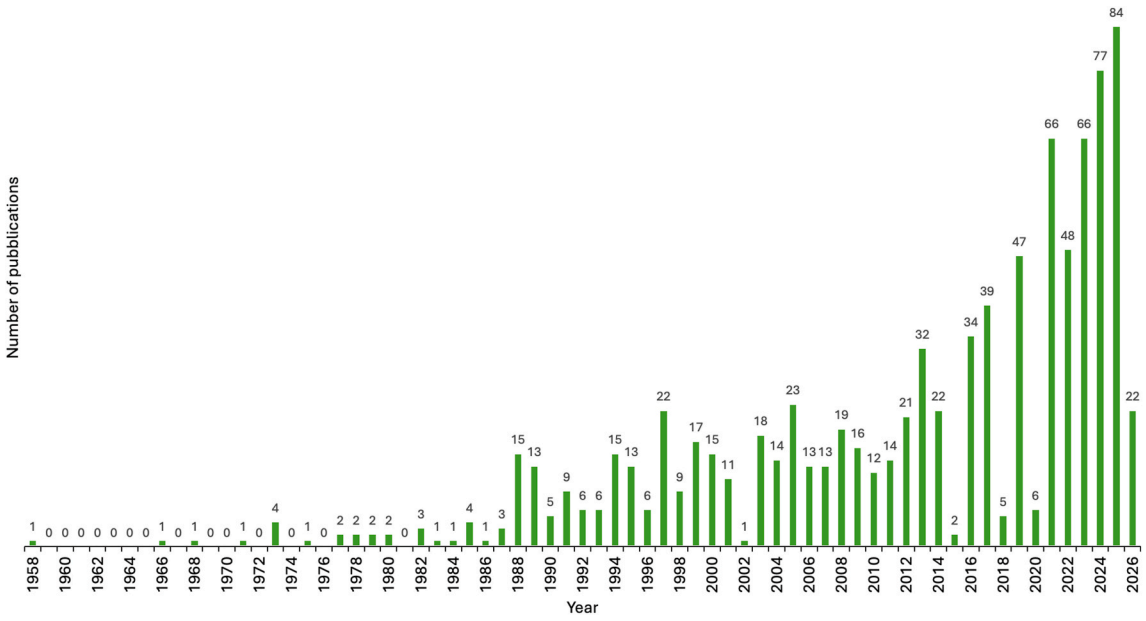

Fig. 4. Publications per year in PubMed database ([18] last updated on 01.04.2026), using the keyword "diosmin".

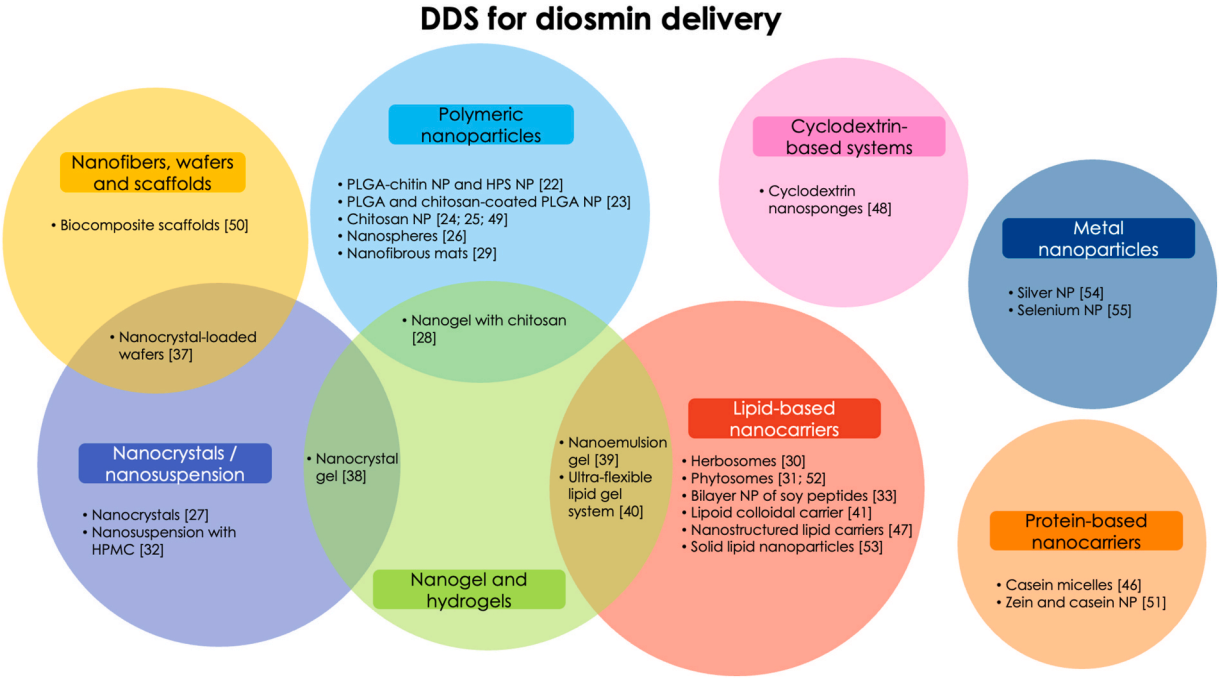

Fig. 5. Summary of the DDS for diosmin delivery discussed in this section, grouped by type basing on their composition, with references reported in square brackets.

influence oral absorption (as described in paragraph 1.2). Herein, the use of DDS could represent a valid strategy since they allow to ameliorate drug solubility and stability, as well as its pharmacokinetic profile by enhancing dissolution rate, protecting from enzymatic and gastric acidic degradation, prolonging the systemic exposure, improving intestinal mucus penetration, etc. [21].

Regarding diosmin oral administration through DDS, different kinds of platforms were found in literature, for the treatment of several pathologies; details about the development of the carriers and their technological characterization are reported in Table 2, while *in vitro* and *in vivo* results are discussed hereafter.

Some polymeric nanocarriers were investigated, such as poly(D,L-lactide-co-glycolide) (PLGA)-chitin nanoparticles (NP), and for hydroxypropyl starch (HPS) NP intended for the treatment of diabetes [22]. *In vivo* studies performed on diabetic rats demonstrated the efficacy of the treatment in stimulating insulin production, thus achieving anti-inflammatory and antioxidant effects, and ameliorating the lipid profile; moreover, histopathological analysis highlighted the improvement of vascular tissues. Both the NP carriers enhanced the activity of diosmin against diabetic atherosclerosis, when compared to the drug alone.

PLGA NP (with or without chitosan coating) were also developed for the oral treatment of ulcer, basing on diosmin ability to inhibit matrix metalloproteinase-9 (MMP-9) upregulation and damage in the mitochondria [23]. *In vivo* mucoadhesion studies were performed on rats via scanning electron microscope (SEM) examinations of stomach and

Table 2
DDS for oral administration of diosmin.

DDS for oral administration	Composition, description and preparation technique – *Therapeutic target*	Technological characterization	Reference
- poly(D,L-lactide-co-glycolide) (PLGA)-chitin NP - hydroxypropyl starch (HPS) NP	- PLGA-chitin NP: produced via emulsion-solvent evaporation. - HPS NP: produced via acid-base neutralization. *Treatment of diabetes.*	- size: 120 nm for PLGA-chitin NP 220 nm for HPS NP. - ZP: +30 mV for PLGA-chitin NP, −33 mV for HPS NP. - Encapsulation efficiency % (EE%): 84.5% for PLGA-chitin NP and 75.9% for HPS. - Morphology via SEM and shape via TEM: spherical for PLGA-chitin NP and HPS NP.	[22]
- PLGA NP - Chitosan-coated PLGA NP	- Produced via emulsion-solvent evaporation method. *Treatment of ulcer.*	- Size: 155.90 nm for PLGA NP; 337.60 nm for chitosan-coated PLGA NP. - PDI: 0.20 for PLGA NP; 0.30 for chitosan-coated PLGA NP. - ZP: −10.50 mV for PLGA NP; +27.40 mV for chitosan-coated PLGA NP. - EE%: 75.30% for PLGA NP; 67.40% for chitosan-coated PLGA NP. - Shape via TEM: both spherical. - Morphology via SEM: solid dense core eventually surrounded by a chitosan shell. - Release: rapid and sustained for both.	[23]
- Chitosan NP	- Chitosan NP produced via ionic gelation using sodium tripolyphosphate (STPP). *Treatment of polyarthritis.*	- Size: 136.1 nm for blank NP; 223.0 nm for loaded NP. - PDI: lower than 0.7 for loaded NP. - ZP +20 mV for blank NP; +2.9 mV for loaded NP. - EE%: 70%. - Morphology via SEM: spherical. - Release: up to 10 h following erosion mechanism.	[24]
- Chitosan NP	- Chitosan NP produced via ionic gelation employing tripolyphosphate (TPP) solution. *Treatment of doxorubicin-induced cardiotoxicity*.	- Size: 210.9 nm for blank NP; 251.1 nm for loaded NP. - PDI: 0.246. - ZP: −33.8 mV for blank NP; −28.4 mV for loaded NP.	[25]
- Nanospheres	- Composed of gliadin and functionalized with lactoferrin. - Produced via nanoprecipitation and spray-drying. - Co-delivered with celecoxib. *Treatment of hepatocellular carcinoma.*	- Size: 220.3 nm. - PDI: 0.252. - ZP: +4.3 mV. - EE%: 95.5% (celecoxib 88.0%). - Shape via TEM: spherical with smooth surface. - Release: slow (28.49% in 24 h), compared to rapid release of free diosmin (100% in 6 h).	[26]
- Nanocrystals	- Composed of Poloxamer 188 (PLX188), with and without chitosan (CS). - The production technique was a combination of bottom-up antisolvent precipitation and top-down probe sonication. *Treatment of hepatic injury.*	- Size: 350.20 nm without CS; 368.93 nm with CS. - PDI: 0.24 without CS; 0.23 with CS. - ZP: −25.93 mV without CS; +40.43 mV with CS. - Shape via TEM and morphology via SEM: rods with smooth surface, eventually surrounded by chitosan layer. - Release: controlled for both.	[27]
- Nanogel	- Produced with chitosan and sodium tripolyphosphate at 1:1 ratio, through ionic gelation method.	- Size: 113.07 nm. - PDI: 0.266. - ZP: +22.32 mV. - EE%: 81.56%. - Shape via TEM: roughly spherical. - Release: slow release reaching almost 80% after 12 h.	[28]
- Nanofibrous mats	- Composed by hydroxypropyl cellulose (HPC), polyvinyl alcohol (PVA), and polyethylenoxide (PEO). - Produced via electrospinning.	- Size via SEM: nanometric. - EE%: ~30%. - Release: peak (50% released) was detected after 10-15 min.	[29]
- Herbosomes	- Composed of soy phosphatidylcholine (PC) and LIPOID® S 75, the complex was prepared using different drug:phospholipid ratios, at different reaction time and temperature.	- EE%: 71.94%.	[30]
- Phytosomes	- Composed of soybean phospholipid (SPC). - Produced via solvent evaporation, salting out, and lyophilization. *Treatment of colon and hepatocellular carcinoma.*	- Size: 316 nm. - PDI: 0.50. - ZP: −27.1 mV. - EE%: 28.40%. - Shape via TEM: well-formed vesicles.	[31]
- Nanosuspension	- Composed of hydroxypropylmethyl-cellulose (HPMC). - Produced via acid base neutralization and anti-solvent precipitation.	- Size: 336 nm for HPMC nanosuspension; 392 nm for its dried form. - PDI: 0.508 nm for HPMC nanosuspension; 0.624 for its dried form. - Shape via TEM: oval, surrounded by a layer when HPMC was used. - Morphology via SEM: irregular and aggregated without stabilizer; separated crystals with HPMC.	[32]

(*continued on next page*)

Table 2 (*continued*)

DDS for oral administration	Composition, description and preparation technique – *Therapeutic target*	Technological characterization	Reference
- Bilayer NP	- Composed of soy peptides and coated with trimethyl chitosan (TMC). - The NP were prepared by enzymatic digestion, followed by ultrasonication.	- Size: ~95 nm for non-coated; ~250 nm for TMC coated. - PDI: ~0.193 for non-coated; ~0.330 for TMC coated. - ZP: ~-25 mV for non-coated; ~+14 mV for TMC coated. - EE%: ~97% for non-coated; ~87% for TMC coated. - Shape: nearly spherical (TEM).	[33]

duodenum, after the oral administration of free diosmin, uncoated and coated diosmin-loaded NP. As expected, free diosmin was not identified either in stomach or duodenum after 8 h. Uncoated formulation demonstrated to be non-mucoadhesive since it was identified in duodenum, while the presence of chitosan (CS) in the coated NP guaranteed the gastric retention due to the interaction with mucus having a negative charge. Furthermore, the anti-ulcer potential was examined pretreating the rats with free diosmin, uncoated and coated loaded NP for 5 days, followed by the induction of gastric ulcer through the intragastric administration of ethanol 70%. The macroscopical and histopathological evaluation of ulcerations, congestion and edema was moderate for free diosmin, mild for uncoated NP, and normal for coated NP, in accordance with their mucoadhesiveness and due to the ability of the CS-coated NP to escape from endosomes and lysosomes thus being uptaken into the cytoplasm. The immunohistochemical localization of gastric NF-κB in glandular and non-glandular gastric tissues demonstrated that the pretreatment with free diosmin and uncoated NP produced moderate expression, while coated NP produced mild expression. Finally, transmission electron microscopy (TEM) analysis of gastric mucosa showed slight amelioration of mucosal cells with free diosmin and uncoated NP, and a pronounced amelioration with coated NP. The coated platform resulted promising for the oral administration of diosmin.

CS NP containing diosmin were also developed in order to exploit the anti-inflammatory potential in the treatment of polyarthritis [24]. The *in vivo* studies performed on edema rat models (inflammation induced by carrageenan and xylene) demonstrated that the anti-inflammatory activity of diosmin was enforced by CS, which also possess anti-inflammatory properties, resulting also in ameliorated weight loss compared to free diosmin and methotrexate. The achievement of the scope was also confirmed by the quantification of some mediators: liver protection was confirmed by the levels of alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), urea and creatinine; reduction of oxidative stress was demonstrated by SOD, CAT and malondialdehyde (MDA) levels; anti-inflammatory potential was verified analyzing the expression of IL-4, IL-10, IL-6, COX-2, TNF-α and NF-κβ. Finally, histopathological evaluation on sciatic nerve and ankle joints confirmed the potential application of this platform for the treatment of polyarthritis.

Another CS platform was developed to benefit from diosmin cardioprotective properties in the treatment with doxorubicin, which is known to produce myocardial damage [25]. The produced carrier was tested *in vivo* on male Wistar rats administrating it through gastric tube, and comparing the result to the control group and the groups treated with: diosmin; doxorubicin; diosmin and doxorubicin. The treatment with diosmin (both free and delivered) reduced serum creatine kinase (CK), MB isoenzyme (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin T (cTnT), and increased Na+/K + -ATPase activity; moreover, the histopathological analysis of heart tissues demonstrated the superior cardioprotective activity of the loaded NP. Furthermore, inflammation produced by doxorubicin was counteracted as demonstrated by the quantification of NF-κB, TNF-α, IL-1β, and IL-10 in the heart. Apoptotic biomarkers Bcl-2-associated X protein (Bax) and caspase-3 activity were reduced, while B cell lymphoma-2 (Bcl-2) level was increased. Finally, the cardiac antioxidant activity of diosmin, especially when encapsulated into CS NP, was confirmed by the quantification of parameters as MDA, nitric oxide (NO), glutathione (GSH), SOD, CAT, GPx, and glutathione reductase (GR). This interesting research article emphasizes once again that the encapsulation into delivery systems can increase the effectiveness of diosmin.

Gliadin nanospheres functionalized with lactoferrin were proposed as dual carrier to deliver diosmin and celecoxib for the oral treatment of hepatocellular carcinoma [26]. Despite a slow release of the two drugs from the dual carrier (probably caused by hydrophobic interactions among them), it was reported an increased IC_{50} value in human hepatocellular cells (HepG2) liver cancer cells treated with different amounts of the dual carrier, compared to the carrier containing a single molecule, highlighting a synergistic effect; this suggests that the slow release reduces the activation of the efflux pump thus avoiding drug resistance. The internalization of the functionalized carrier confirmed the increased cytotoxic activity thanks to the targeting effect of the lactoferrin coating. These results were confirmed with *in vivo* studies on mice, quantifying several tumoral biomarkers and demonstrating the potential application of lactoferrin functionalized gliadin nanospheres containing diosmin and celecoxib, for the oral treatment of hepatocellular carcinoma.

Nanocrystals composed of Poloxamer 188, with and without CS, for the delivery of diosmin were developed for the oral treatment of hepatic injury [27]. *In vivo* analyses were performed on rats in which ferrous sulfate hepatic injury was induced before or after the oral treatment with diosmin nanocrystals. Different biomarkers were quantified in the blood (AST; ALT; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; LDH; TC, total cholesterol; ALB, albumin; TB, total bilirubin; MDA; GSH; NOx, nitrate/nitrite production) and a great regulation of their levels was reported using the loaded CS-poloxamer nanocrystal platform. This result, also confirmed through histopathological and immunohistochemical analyses, is attributable to the ability of the carrier to increase diosmin solubility as well as to enhance permeability and mucoadhesion on intestine cells, especially in the post-treatment experimental conditions.

Nanofiber encapsulating diosmin were produced using hydroxypropyl cellulose (HPC), polyvinyl alcohol (PVA), and polyethylenoxide (PEO) as a strategy to increase oral bioavailability of the drug [29]. Different amounts of diosmin were loaded into the nanofiber mats, and the preliminary *in vivo* bioavailability study demonstrated that the nanofibers guarantee an increase in the initial plasma levels, comparing to the free diosmin.

Herbosomes were developed screening different phospholipids and the optimal formulation (composed of soy phosphatidylcholine (PC) and LIPOID® S 75) was tested in beagle dogs comparing to the commercially available medicine [30]. The results of the *in vivo* tests demonstrated that the slower metabolization of the phospholipids compared to the commercial formulation guarantees a higher bioavailability thus a greater permeation across biological barriers.

Soybean phospholipid phytosomes for the oral delivery of diosmin

were analyzed in order to assess the gastrointestinal stability and permeability [31]. The *in vitro* stability was investigated incubating the nanocarrier with simulated gastric fluid at pH 1.2 for 2 h and with simulated intestinal fluid pH 7.4 for 6 h; the analysis of size and polydispersity index (PDI) demonstrated not relevant changes, thus confirming a great stability without the occurrence of aggregation or precipitation phenomena. The changes in zeta potential (ZP) values were related to the dual charge of the soya phosphatidylcholine, thus the carrier demonstrated a great stability in the gastrointestinal environment. *Ex vivo* permeation studies through noneverted gut sac technique using Wistar rats showed a great enhancement of intestinal absorption of diosmin delivered using phytosomes (up to 80% in 2 h) when compared to the free drug (0% throughout the whole experiment), confirming the advantage of the use of DDS to ensure the bioavailability of the molecule.

The same research group also developed nanosuspensions of hydroxypropylmethyl-cellulose (HPMC) to deliver diosmin, which were tested for *ex vivo* permeation studies as previously described [32]. The nanosuspension demonstrated an 89% permeation in 2 h compared to the free drug which was 0%; the spray-dried form of the nanosuspension was absorbed for 65.7% in 2 h, while the addition of mannitol in the matrix of the dried carrier increased the permeation to 72.7% confirming that the solubility is the key-point for a successful intestinal absorption.

In vitro digestion of soybean-CS bilayer NP loaded with diosmin (produced using of soy peptides and coated with trimethyl chitosan (TMC)) showed a significant increase of drug release from NP when compared to the very low release of free diosmin in both gastric and intestinal simulated fluids [33]. Moreover, *ex vivo* permeation of diosmin through Sprague-Dawley (SD) rat intestines showed the bioaccessibility of over 50% of the drug delivered in the bilayer NP compared to the free diosmin which was lower than 5%.

Cyclodextrins were also reported to be used for the oral administration of diosmin. *In vitro* dissolution experiments demonstrated that the inclusion of diosmin into 2-hydroxypropyl-β-cyclodextrin (HPβCD) increased the dissolution to 82.8% and 64.0% in 2 h, compared to 18.2% of the free drug [34]. *In vivo* studies on SD rats confirmed a notably increased solubility of diosmin after inclusion into γ-cyclodextrin, ameliorating also pharmacokinetic parameters such as maximum plasma levels and rapidity of plasma peak [35].

2.2. Dermal administration

Dermal administration of diosmin was also investigated, for the possibility to avoid gastrointestinal and hepatic metabolisms [36]. Several physicochemical and molecular characteristics of the drug influence its efficient penetration of the stratum corneum (the main barrier to dermal administration): lipophilicity, molecular weight, solubility, pKa, chemical stability (as described in paragraph 1.2; detailed insights could be found elsewhere [36]). For these reasons, the employment of DDS allows to ameliorate solubility and permeability, as well as to improve chemical stability and release of the drug. In particular, the nanosystems could maintain the ionization state of the encapsulated drug improving its permeation, or could interact with the stratum corneum facilitating the penetration; moreover, they could protect the drug from degradation and provide controlled and sustained release over time [36]. As a consequence, dermal formulations should be produced with due consideration to viscosity and surface tension, hydrophilic-lipophilic equilibrium, phase transition occurrence, etc. [36].

Dermal administration of diosmin could be useful for different therapeutic applications, thus various platforms were developed in order to overcome the limit of its poor drug absorption through the skin. The technological characterization of these carriers is reported in Table 3, while *in vitro* and *in vivo* studies are discussed below.

Diosmin nanocrystals were loaded into sodium alginate and gelatin wafers for the ability of the wafer structure to guarantee the adhesion to the skin and the protection of the wound, for the treatment of diabetic ulcer [37]. *In vivo* wound healing studies on diabetic rats were carried out comparing wafers loaded with diosmin nanocrystals (70.7% healed) or diosmin powder (28.13% healed), and gels with diosmin nanocrystals (56.66% healed) or diosmin powder (28.00% healed). The obtained results confirmed the improvement of diosmin therapeutical efficacy thanks to the adherence and protection provided by the wafer structure; moreover, the employment of nanocrystals to deliver the drug results in high drug dose at the therapeutical site, thus promoting faster and improved wound healing.

Nanocrystals containing diosmin were also developed as a topical gel for the treatment of psoriasis, and the materials used were hydroxypropyl methyl cellulose (HPMC E15), methyl cellulose (MC), and Poloxamer 407 [38]. *In vivo* studies on SD rat with induced psoriasis used a treatment with diosmin powder gel or different doses of diosmin nanocrystal gels for 13 days. The evaluation of psoriasis area severity index (PASI) showed similar values for non-treated and powder gel treated groups, while nanocrystal gels showed a significant dose-related improvement of the parameters. Moreover, the quantification of the levels of inflammatory cytokines in serum and the evaluation of the proliferation of keratinocytes in psoriatic tissue confirmed the ability of diosmin nanocrystal gel to modulate molecules such as TLR7, 8/NF-κB/micro RNA-31, AKT/mTOR/P70S6K and Tregs/Th17, thus improving psoriatic pathological condition.

A gel with diosmin nanoemulsion was developed using experimental design in order to be used for wound healing purposes; the nanoemulsion was prepared using LG90® oil, Tween 80 and Transcutol HP, and the gel was then obtained using carbopol and methylparaben [39]. After assessing acute *in vivo* dermal toxicity of the produced carrier, its ability to promote wound closure was evaluated comparing to negative control with base gel and to positive control with fusidic acid gel, demonstrating similar results at all the analyzed timepoints. A microscopic evaluation of the tissues highlighted that, despite both nanoemulsion gel and fusidic acid gel were able to restore the collagen fibres elasticity, the positive control group tissue still showed signs of degeneration and necrosis, while the tissue treated with the nanocarrier appeared almost healthy. Moreover, nanoemulsion gel was able to produce a higher anti-inflammatory activity on *in vivo* carrageenan-induced paw edema, suggesting a promising application of the formulation in the treatment of wounds.

A carbopol gel system was developed with ultra-flexible nanosuspension of diosmin (produced with lecithin, cholesterol and Tween 80), for varicose vein application [40]. In details, the optimal nanosuspension was obtained through experimental design in order to define the quali-quantitative composition. After a deep technological characterization, the skin permeation was investigated comparing the diosmin ultra-flexible gel, the diosmin ultra-flexible lipid nanosuspension and the diosmin base gel. The quantification of drug permeation in 12 h (900 μg cm^2 for the nanosuspension gel, 795 μg cm^2 for the nanosuspension, and 500 μg cm^2 for the base gel) highlighted that the deformability of the carrier has a great influence, and also that the gel further improves the permeation due to the increased residence on the target site. This result was confirmed by the percentages of skin retention, which were 83.44% for the nanosuspension gel, 55.5% for the nanosuspension, and 66.39% for the base gel.

Lipoid colloidal carriers composed of different essential oils were produced to encapsulate diosmin for the potential dermal photoprotection [41]. *In vitro* 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay demonstrated the highest antioxidant activity for the carrier produced with essential oils in comparison with the one produced with liquid paraffin (*Rosmarinus officinalis* > *Vitis vinifera* > *Zingiber officinale* > liquid paraffin); the *in vitro* photo-protective test has led to the same affirmation, but with the highest activity for *Zingiber officinale*, followed by *Vitis vinifera*, *Rosmarinus officinalis* and again finally liquid paraffin. *In vivo* analysis of solar photo-protection was performed

Table 3
DDS for dermal administration of diosmin.

DDS for dermal administration	Composition, description and preparation technique – *Therapeutic target*	Technological characterization	Reference
- Nanocrystal-loaded wafers	- Nanosuspension produced with hydroxypropyl methyl cellulose (HPMC E15) or methyl cellulose (MC) via antisolvent precipitation technique. - Nanocrystals produced with sodium alginate (SA) and gelatin (GE) via antisolvent method. - Wafers produced through thickening method or dried nanocrystal method. *Treatment of diabetic ulcer.*	- Size: 276.9 nm for non-lyophilized nanosuspension; 304.0-308.2 nm for lyophilized nano-suspension; 321.1-358.4 nm for nanocrystals. - PDI: 0.43-0.60. - Morphology via SEM: wafers with highly porous structure. - Shape via TEM: spherical. - Release: sustained over 480 min.	[37]
- Nanocrystal gel	- Prepared using anti-solvent precipita-tion technique with hydroxypropyl methyl cellulose (HPMC E15), methyl cellulose (MC), Poloxamer 407. *Treatment of psoriasis.*	- Size: 276.9 nm for the nanocrystals; 320.5 nm for the nanocrystal gel. - PDI:0.43 for the nanocrystals. - Release: 10% in 3 h using pH 10 medium; 25% in 24 h using pH 9 medium.	[38]
- Nanoemulsion-Based Gel	- Nanoemulsion composed of LG90® oil, Tween 80 and Transcutol HP, by spontaneous emulsification method. - Nanoemulsion gel prepared adding carbopol and methylparaben to the nanoemulsion. *Treatment of wounds.*	- Size: 41 nm for the nanoemulsion. - PDI: 0.073 for the nanoemulsion. - ZP: −23.4 for the nanoemulsion. - EE%: 87% for the nanoemulsion. - Shape via TEM: spherical for the nanoemulsion. - Release: at 24 h, about 70% released from the gel, almost 60% released from the nanoemulsion, almost 30% released from the diosmin suspension.	[39]
- Ultra-flexible lipid gel system	- Diosmin-loaded ultra-flexible lipid nanosuspension produced with soy lecithin, choles-terol and Tween 80, by thin-film hydra-tion method. - Nanosuspension incorporated into carbopol gel. *Treatment of varicose veins.*	- Size: 144.56 nm for the nanosuspension. - PDI: 0.397 for the nanosuspension. - ZP: −24.5 mV for the nanosuspension. - EE%: 84.09% for the nanosuspension. - Shape via TEM: smooth and with round edges for nanosuspension. - Release: sustained for the gel (85.14% in 12 h) and burst for nanosuspension (62.37% in 12 h) and base gel (44.84% in 12 h).	[40]
- Lipoid colloidal carrier	- Lipoid colloidal carriers prepared with different oils: liquid paraffin; *Rosmarinus officinalis* (rosemary essential oil), *Zingiber officinale* (ginger essential oil) and *Vitis vinifera* (grape seed essential oil). - The preparation method used was the probe sonication. *Dermal photo-protection.*	- Size: 144.3 nm for paraffin carrier; 121.1 nm for rosemary carrier; 121.6 nm for ginger carrier; 123.3 nm for grape seed carrier - PDI: 0.240 for paraffin carrier; 0.229 for rosemary carrier; 0.253 for ginger carrier; 0.252 for grape seed carrier. - ZP: −29.0 mV for paraffin carrier; −31.9 mV for rosemary carrier; -28.1 mV for ginger carrier; -31.9 mV for grape seed carrier - EE%: 103.53% for paraffin carrier; 102.92% for rosemary carrier; 102.91% for ginger carrier; 101.56% for grape seed carrier. - Shape via TEM: spherical.	[41]

on Swiss albino mice treated with the carriers and exposed daily to the sun for 7 days; the histological analysis of skin demonstrated the beneficial effects of all the samples, with greater efficacy obtained with the lipoid carriers produced with essential oils, confirming their synergistic effect with the encapsulated diosmin. In particular, the lipoid carrier containing diosmin and rosemary essential oils showed the highest antioxidant and anti-ageing activity, while the carrier produced with diosmin and ginger oil produced the greatest UV-blocking effect.

Cyclodextrins were also used to include diosmin into a Carbopol gel and tested *in vivo* for the potential topical application for the treatment of muscle mechanical trauma [42]. The administration of diosmin β-cyclodextrin gel and ultrasounds on Wistar rats demonstrated to be more effective in decreasing lipid peroxidation and oxidative cytokines than ultrasounds and saline gel, or only diosmin gel.

2.3. Other administration routes

Considering the various therapeutical applications of diosmin, administration routes, such as parenteral and ocular, could be considered.

Parenteral administration represents the route with the highest bioavailability, thus, despite the scarce patient compliance and the need of specialized personnel, it is selected for drugs with low therapeutic index and low bioavailability [43]. In this regard, since the quick onset of action is also associated with short half-life, the use of DDS can prolong drug activity reducing the number of injections, with a consequent reduction of the side effects (detailed insights could be found elsewhere [43]).

Ocular topical administration, despite being largely used, presents several limitations associated to the complex anatomical structure of the eye [44]. After topical ophthalmic instillation, the main barriers encountered are the tears film with the blinking reflex, and the cornea [45]; the low solubility of the drug could represent an additional limit to a successful ophthalmic treatment (detailed insights could be found

elsewhere [44], [45]). Herein, the advantages of DDS employment are the possibility to prolong the residence time on ocular surface through mucoadhesive systems, protect the drug from degradation, enhance drug permeation, guarantee prolonged release while avoiding invasive treatments [44].

Basing on these premises, in Table 4 are reported the publications concerning parenteral and ocular DDS containing diosmin

The parental treatment with diosmin – in association with berberine and loaded into casein micelles – was investigated as a potential treatment for hepatocellular carcinoma [46]. Two functionalizations were considered: lactobionic acid and folic acid. After assessing the compatibility with parenteral administration evaluating hemolysis and serum stability, *in vitro* assays demonstrated the ability of the dual drug-dual targeted platform of inducing cytotoxicity on HepG2 human liver cancer cells and of being uptaken in a higher amount compared to the single targeted carriers. Moreover, *in vivo* studies were performed on mice, comparing the free drugs and their combination with the dual loaded-non targeted, the single targeted and the dual targeted carriers. It emerged a higher anti-tumoral activity for the dual loaded-dual targeted platform (through the activation of caspase 3 and the inhibition of VEGF, TNF-α, NF-κB, and COX-2), which resulted to improve liver reparation.

Ocular application was also evaluated developing a nanostructured lipid carrier (NLC) platform for the potential treatment of diabetic retinopathy [47]. The optimized nanocarrier, composed of Softisan® 100, Capryol® 90, and Tween 80, was investigated *in vitro* on retinal pigment epithelial cells (RPECs) demonstrating that the reduced viability caused by increasing amounts of diosmin could be prevented by the encapsulation in NLC. Moreover, studies on human retinal pigment epithelial cell line (ARPE-19) were performed in order to assess the ability of decreasing ocular inflammation produced by TNF-α; it resulted that diosmin NLC was able to invert the cytotoxicity produced by the proinflammatory cytokine. This result can also explain the reduced cytotoxicity of diosmin when incapsulated into NLC.

Table 4
DDS with diosmin for other administration routes.

DDS for other routes of administration	Composition, description and preparation technique – *Therapeutic target and route of administration*	Technological characterization	Reference
- Spray-dried micelles	- Micelles composed of casein and produced via spray-drying. - Delivering both diosmin and berberine. - Functionalized with lactobionic acid and folic acid. *Treatment of hepatocellular carcinoma through parenteral administration.*	- Size: 186.7-295.4 nm for spray-dried micelles; 253.1 nm after resuspension. - PDI: 0.34-0.45 for spray-dried micelles. - ZP: −22 to −29.6 mV for spray-dried micelles; −26 mV after resuspension. - Shape via TEM: spherical with smooth surface. - Release: after 24 h, 23% released from micelles, and 3.5% released from free diosmin.	[46]
- Nanostructured lipid carrier	- Produced by melt emulsification method followed by ultrasonication. - Composed of Softisan® 100, Capryol® 90, and Tween 80, and optimized through Experimental Design. *Treatment of diabetic retinopathy through ocular administration.*	- Size: 85.33 nm. - PDI: 0.263. - ZP: −18.5 mV (loaded NLC showed similar values). - Shape via TEM: round NP with oily core.	[47]

2.4. Miscellaneous

Some research articles reported in literature investigated diosmin delivery by different platforms, without specifying the intended administration route or the target pathology. Herein, we discuss these research papers in order to present the technological advantages (Table 5) achieved by the use of DDS in terms of *in vitro* and *in vivo* performances.

Binary and ternary complexes with β-cyclodextrin were obtained to increase the amount of the incorporated cyclodextrin into the final product [56]. The polymers used for the complexation by kneading method were polyethylene glycol 6000 (PEG 6000) and HPMC. *In vitro* antioxidant activity was assessed using DPPH, confirming the scavenging activity of diosmin and demonstrating its enhancement when included into cyclodextrins probably due to the increased drug amount into the binary and ternary complexes. The same research group also developed diosmin-loaded cyclodextrins which were cross-linked into nanosponges by diphenylcarbonate, for the potential treatment of breast cancer [48]. DPPH *in vitro* assessment confirmed the superior scavenging activity of the nanosponges compared to free diosmin. The cell viability, tested on MCF-7 breast cancer cell line, was dose-dependent for both the drug and the nanosponges and statistically more significant for the latter, and the pro-apoptotic potential of diosmin was enhanced when encapsulated into the carrier.

CS NP carrier was developed to encapsulate diosmin and other natural phenols (eriocitrin, hesperidin, sinapic acid, catechin, coumaric acid, neohesperidin, naringenin), extracted from *Persian lemon* (*Citrus latifolia*) waste, to be used for food application [49]. The antioxidant activity assessment was performed by DPPH and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assays, demonstrating a slight activity for the unloaded NP (related to the CS structure) and an increased efficacy of the loaded NP compared to the free waste extract, thus the CS NP and the loaded extract together exerted a synergistic effect. Moreover, the antibacterial activity was evaluated on *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhimurium* measuring the minimum inhibitory concentration (MIC, μg/ml) and the percentage of inhibition (I%): for free extract, the MIC was 21.17-28.22 μg/ml and the I% was 3.54-4.72%; for unloaded NP the MIC was 15.00-25.00 μg/ml and the I% was 4.00-6.66%; for the loaded-NP the MIC was 10.31 μg/ml and the I% was 9.69%. These results demonstrated the antimicrobic activity of the diosmin-loaded CS NP and suggested a synergistic effect between the loaded phenol and the NP materials, especially for *Escherichia coli* and *Salmonella typhimurium*.

Diosmin was encapsulated into a gelatin and nanohydroxyapatite (nHAp) scaffold, in order to assess its potential application for osteostimulatory purposes [50]. The *in vitro* cytocompatibility of the drug-loaded scaffold was confirmed on C3H10T1/2 mouse mesenchymal stem cells. The osteogenic potential activity was *in vitro* evaluated trough the expression of osteoblast transcription and differentiation marker genes, which were up-regulated by the diosmin-scaffold; moreover, this was confirmed also by *in vivo* studies on rat tibial bone defective model, which showed bone regeneration effects.

Faezi and coworkers developed nanoparticulate platform composed of zein and casein proteins for the delivery of diosmin in the treatment of ovarian cancer [51]. The *in vitro* MTT cytotoxicity assay demonstrated that the formulation was safe on HDF (normal human dermal fibroblasts) cell line, while it decreased cell viability on A2780 ovarian cancer cell line. Furthermore, flow cytometry test on cancer cells showed a dose-dependent apoptosis. This result was also confirmed by

Table 5
Miscellaneous DDS with diosmin.

Miscellaneous DDS	Composition, description and preparation technique – *Therapeutic target*	Technological characterization	Reference
- Cyclodextrin nanosponges	- Diosmin loaded β-cyclodextrins were crosslinked into nanosponges by diphenylcarbonate. *Treatment of breast cancer.*	- Size: 412 nm. - PDI: 0.259. - ZP: −10,8 mV. - DL%: 88.7%. - Morphology via SEM: porous and spherical. - Release: sustained for the nanosponges (99.2% at 12 h), compared to diosmin suspension (44.4% at 12 h).	[48]
- Chitosan NP	- Chitosan NP produced via ionic gelation using STPP. *Food applications.*	- Size: 232.7 nm. - PDI: 0.182. - ZP: −3.8 mV. - EE%: 81.16%.	[49]
- Scaffolds	- Biocomposite scaffold produced via freeze-drying using gelatin and nanohydroxyapatite (nHAp). *Treatment of bone damage.*	- Size: 20 mm diameter and 5 mm thickness for the scaffolds; 80-100 μm pore diameters. - Morphology via SEM: interconnected porous structure. - Release: burst effect and then sustained release.	[50]
- Protein NP	- Composed of zein (a corn protein) and casein (a milk protein) and produced by antisolvent precipitation method. *Treatment of ovarian cancer.*	- Size: 265.30 nm. - PDI: 0.21. - EE%: 93.45%. - Morphology via SEM: smooth surface.	[51]
- Phytosomes	- Phospholipid complexes of diosmin prepared via solvent evaporation technique. - As a phospholipid, the phosphatidylcholine was employed.	- Size: 233.4 nm. - PDI: 0.642 nm. - EE%: 94.08%. - Morphology via SEM: drug entrapped in the phospholipid structure. - Release: after 12 h, 89% released from the phytosomes, compared to 44% from the free diosmin.	[52]
- Solid lipid nanoparticles	- SLN prepared via hot homogenization technique using Compritol ATO 888, soy lecithin and Tween 80, and through Experimental Design. - SLN were lyophilized after the addition of trehalose. *Treatment of hepatocellular carcinoma.*	- Size: 37.48 nm. - PDI: 0.29. - EE%: 73.46%. - Shape via TEM and morphology via SEM: spherical form. - Release: biphasic release, with an initial burst effect.	[53]
- Silver NP	- Silver NP, loaded with diosmin and prepared via green synthesis method with flavonoid solution, were compared to NP produced with hesperidin and naringin. *Treatment of cancer.*	- Size: 5-40 nm. - Shape via TEM: hexagonal.	[54]
- Selenium nanospheres	- Selenium nanospheres were prepared using green synthesis method, employing Arabic gum and encapsulating diosmin and luteolin. *Treatment of type 2 diabetes mellitus.*	- Size: 47.84 nm. - PDI: 0.208. - ZP: −17.6 mV. - EE%: 86.1%. - Shape via TEM: spherical. - Release: initial burst effect followed by a slow release.	[55]

real-time PCR, which highlighted the upregulated expression of apoptotic genes p53, caspase 8, and caspase 9, suggesting the potential application of this platform in cancer treatment. Moreover, the antioxidant potential was evaluated by ABTS and DPPH free radical assays, showing a greater activity towards ABTS especially at the higher concentrations tested.

Phosphatidylcholine phytosomes were developed complexing diosmin and phosphatidylcholine in order to improve the solubility thus the bioavailability of the drug [52]. In this preliminary research, the aim was achieved as demonstrated by the dissolution and the permeation studies, suggesting an enhanced absorption of the drug.

Solid lipid nanoparticles (SLN) containing diosmin were developed as a potential anticancer treatment for hepatocellular carcinoma [53]. The nanoparticles were obtained using Compritol ATO 888, soy lecithin and Tween 80. *In vitro* cell viability of human hepatocellular cells (HepG2) was influenced by diosmin loaded-SLN depending on the dose, and the cytotoxicity was higher than the free diosmin. The presence and type of hepatic nodules and the occurrence of hepatic cirrhosis were assessed *in vivo* on hepatocellular carcinoma rat model, demonstrating a higher anticancer activity for the loaded SLN compared to the free diosmin. Moreover, diosmin loaded-SLN demonstrated *in vivo* antioxidant activity though the reduction of lipid peroxidation and the enhancement of the levels of antioxidant enzymes (CAT, SOD, GPx and GST).

As inorganic carrier, silver NP were produced using basic aqueous solution of diosmin, hesperidin or naringin, for anticancer applications [54]. Their antibacterial potential was assessed on *Escherichia coli*, *Pseudomonas putida* and *Staphylococcus aureus*, which showed the following values of zone of inhibition (mm) when using diosmin NP: 6 mm for *E. coli*, 6 mm for *P. putida* and 7 mm for *S. aureus* (the values for $AgNO_3$ were 3, 3.5 and 4, respectively). *In vitro* cytotoxicity on human promyelocytic leukemia (HL-60) cells showed a slight decrease of viability with increasing doses of diosmin silver NP.

Selenium nanospheres with Arabic gum were also developed and loaded with diosmin and luteolin, as a potential therapy for type 2 diabetes mellitus [55]. *In vivo* studies were performed on streptozocin-induced diabetes mice model and the dual loaded-nanospheres were compared to the blank carrier and to the free drugs solution. The antidiabetic activity was assessed analyzing the values of body weight, water intake and food intake, demonstrating better results than metformin positive control. Moreover, the oral glucose tolerance (OGTT) test and the insulin tolerance test (ITT), performed in comparison with glibenclamide, demonstrated a greater reduction in blood glucose levels and an ameliorated insulin resistance, respectively. The antioxidant action of the loaded-nanospheres resulted in the increase of enzymes as CAT, GPx, and SOD; moreover, enzymes predictors of liver damage (AST, ALT, and ALP) were reduced after 6

weeks of treatment, suggesting the potential of this platform to enhance liver repairment.

3. Patents with diosmin and drug delivery systems

In order to evaluate the relevance in technological transfer of the application of diosmin in therapy, the currently published patents were evaluated. A search on the database "Patentscope" ([57] last updated on 01.04.2026) was performed employing the keyword "diosmin"; it should be noted that if the drug is mentioned only in the patent's original language and there is no English translation into "diosmin", it may not have been detected. This search resulted in 425 published patents: 184 are related to pharmaceutical forms of the drug, while the remaining ones address the methods for extraction or purification. Henceforth, only the patents regarding pharmaceutical forms are considered. The increase of research interest in diosmin during the last decade is glaring (Fig. 6a), and it is also interesting to note that China is the Country with the highest number of diosmin patents, immediately behind the international Patent Cooperation Treaty (PCT) office, and followed by the European patent office (Fig. 6b).

Information regarding the pharmaceutical forms' patents is detailed in Table 6. Similarly to literature findings, to date there are only few patents covering the use of DDS for the administration of diosmin. In fact, among the mentioned 184 patents, only 3 of them actually employ delivery platforms: they are reported in Table 6 using bold font (some of them are multiple since were submitted to different offices), and a brief description of the patents' claims is reported below.

The patent entitled "A method of manufacturing a solution of nanoparticles of acetylsalicylic acid or diosmin or drotaverine" was submitted to the international PCT (WO/2018/100413 on the 07/06/2018), the European Patent Office (110372768 on the 09/10/2019), the Polish (3548001 on the 11/07/2022) and the Spanish (2918976 on the 21/07/2022) offices. It regarded a heterogeneous nanosystem obtained by mixing an aqueous lipid phase (containing polymers, surfactants and modifying agents) and non-aqueous lipid phase (containing polymers, fatty acids, and solvents). The obtained system, with an average size lower than 500 nm, was demonstrated to have great stability to aggregation and was claimed to increase diosmin bioavailability and efficacy.

Another patent is entitled "Preparation method and application of diosmin derivative sustained release preparation", submitted to the Chinese patent office (112843243 on the 28/05/2021). It described a hydrogel formulation composed by hyaluronic acid, CS and sodium alginate, where diosmin was encapsulated, addressing the treatment of haemorrhoids, varicose vein and other blood circulation related diseases. The release of diosmin from the platform was obtained through pH-dependent stability; in fact, the preparation remained stable at $pH < 2.5$, guaranteeing no release in the stomach thus reducing the occurrence of side effects, while at $pH > 5$ it slowly degraded producing a sustained release profile in the intestine. *In vivo* studies on male SD rats demonstrated the superior efficacy on venous system compared to free diosmin.

Finally, the patent entitled "Microencapsulated formulation comprising diosmin, toxerutin and coumarins, composition thereof and use thereof for the treatment of circulatory disorders" was submitted to

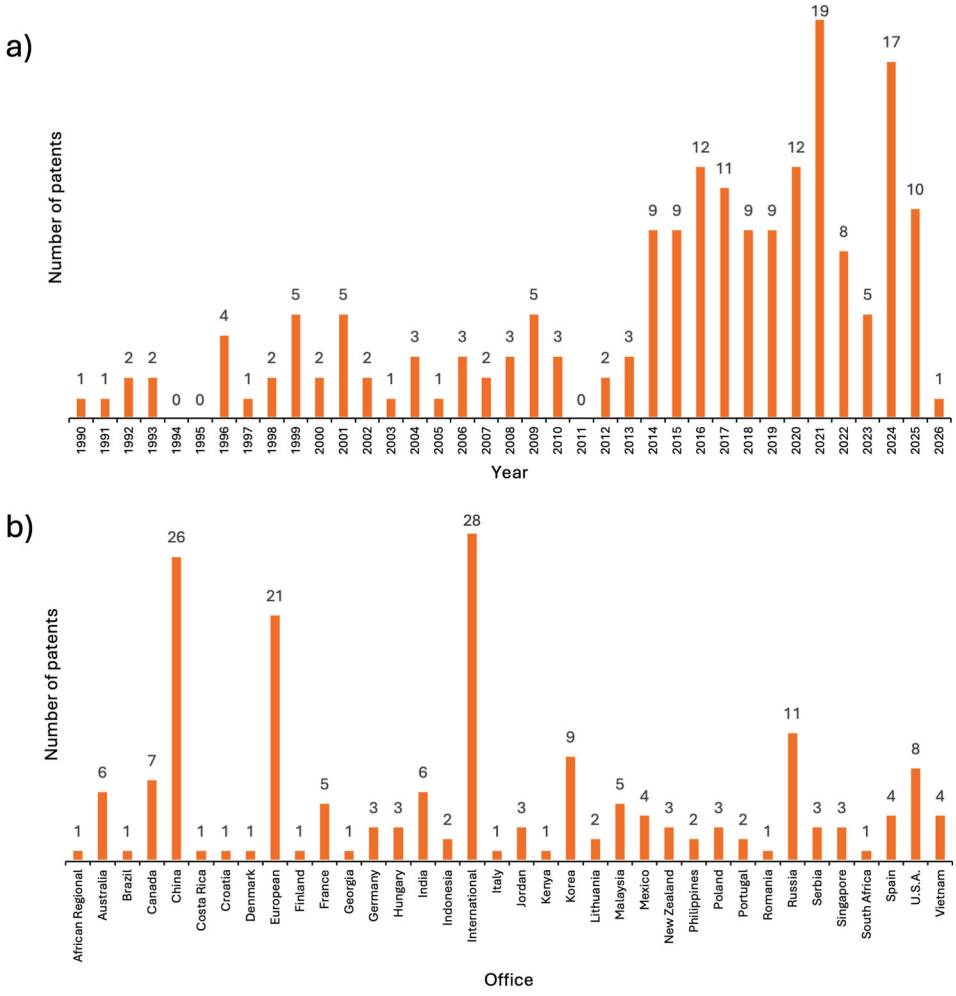

Fig. 6. Number of patents regarding pharmaceutical forms of diosmin, classified per: (a) publication year and (b) office ([57] last updated on 01.04.2026).

Table 6
Patents regarding pharmaceutical form of diosmin ([57] last updated on 01.04.2026); the ones regarding DDS are in bold font.

N°	Title	Code	Office	Publication date
1	Diosmin octakis (hydrogen sulfate) aluminium complex	4894449	U.S.A.	16/01/1990
2	Novel lyophilized form of diosmin and its preparation	2661610	France	08/11/1991
3	Plant-based combination for use against AIDS - contains tannic acid, glycosidecpd., bitter substances, ethereal oils, limonene, m-cresol, etc.	000004120296	Germany	19/03/1992
4	Novel skin preparations having a phlebotonic action and process for preparing them	2668705	France	07/05/1992
5	Composition containing diosmin	541874	European	19/05/1993
6	Topical compounds, having a vascular protecting and veinotonic action - contain diosmin, fatty acid(s), hydrating agent, neutralising agent, gelling agent and opt. stabilisers, preservatives, colours, perfumes, etc.	2692145	France	17/12/1993
7	Composition pharmaceutique pour l'administration de flavonoides	2726469	France	10/05/1996
8	Pharmaceutical composition for the oral administration of flavonoids	0711560	European	15/05/1996
9	Pharmaceutical composition for oral administration of flavonoids	1995/09473	South Africa	31/07/1996
10	Pharmaceutical composition for oral administration of flavonoids	1131538	China	25/09/1996
11	Pharmaceutical composition for oral administration of flavonoids	280418	New Zealand	24/03/1997
12	Use of a pharmaceutical composition for treating and/or preventing ischemia	WO/1998/051291	International	19/11/1998
13	Use of a pharmaceutical composition for treating and/or preventing ischemia	2287363	Canada	19/11/1998
14	Use of a pharmaceutical composition for treating and/or preventing ischemia	1998073272	Australia	28/01/1999
15	Natural substance based agent	WO/1999/048386	International	30/09/1999
16	Preparation based on natural substances	232537	Canada	30/09/1999
17	Cosmetic, dermatological, pharmaceutical, dietetic or food compositions, e.g. for improving skin condition, comprise flavonoid esters	000019922287	Germany	25/11/1999
18	Natural substance based agent	102038782	Australia	09/12/1999
19	Use of a pharmaceutical composition for treating and/or preventing ischemia	0981339	European	01/03/2000
20	Composition comprising diosmin for preventing and treating hyperlipidemia and arteriosclerosis	1020000019719	Korea	15/04/2000
21	Composition containing diosmin useful for preventing and treating arteriosclerosis and hyperlipemia	1020010007625	Korea	26/01/2001
22	Composition containing neohesperidin dihydrochalcone useful for preventing and treating arteriosclerosis, hyperlipemia, liver diseases, and glycosemia	1020010007624	Korea	26/01/2001
23	Composicao farmaceutica para a administracao oral de flavonoides	711560	Portugal	30/10/2001
24	Composicion farmaceutica para la administracion oral de flavonoides	2160145	Spain	01/11/2001
25	Use of buchu extracts for hypertension	2001297027	Australia	20/12/2001
26	Use of buchu extracts for hypertension	WO/2002/020030	International	14/03/2002
27	Use of buchu extracts for hypertension	2425912	Canada	14/03/2002
28	Use of buchu extracts for hypertension	1318826	European	18/06/2003
29	Dry oral phlebotonic and vasculoprotective formulation for the treatment of venous insufficiency, capillary fragility and haemorrhoids, in the pharmaceutical form of a chewable tablet containing diosmin	2003288308	Australia	01/04/2004
30	Dry formulation for easy oral administration of diosmin for use as venotopic agent e.g. in treatment of haemorrhoids, comprising suckable or chewable tablet	2845597	France	16/04/2004
31	Dry oral phlebotonic and vasculoprotective formulation for the treatment of venous insufficiency, capillary fragility and haemorrhoids, in the pharmaceutical form of a chewable tablet containing diosmin	WO/2004/032942	International	22/04/2004
32	Dry oral phlebotonic and vasculoprotective formulation for the treatment of venous insufficiency, capillary fragility and haemorrhoids, in the pharmaceutical form of a chewable tablet containing diosmin	1549326	European	06/07/2005
33	Pharmaceutical dosage form effective at microcirculatory level containing at least one flavonoid	WO/2006/089317	International	31/08/2006
34	Composizione farmaceutica di una tipica frazione microcristallina di flavonoidi	MI20050517	Italy	30/09/2006
35	Pharmaceutical composition	1707192	European	04/10/2006
36	Food composition for functional foods and nutritional supplements	WO/2007/141351	International	13/12/2007
37	Composicion alimentaria funcional rica en compuestos fenolicos y uso de dicha composicion	2288122	Spain	16/12/2007
38	Diosmin solid medicinal formulation	02314812	Russia	20/01/2008
39	Pharmaceutical dosage form effective at microcirculatory level containing at least one flavonoid	1888028	European	20/02/2008
40	Pharmaceutical composition for oral or topical administration comprising microcrystalline flavonoids for treating chronic vein disease	1020080030835	Korea	07/04/2008
41	Food composition for functional foods and nutritional supplements	2022345	European	11/02/2009
42	Pharmaceutical composition combining various venotonic and vasoprotective agents for the treatment of chronic venous insufficiency	WO/2009/031878	International	12/03/2009
43	Pharmaceutical composition combining various venotonic and vasoprotective agents for the treatment of chronic venous insufficiency	MX/A/2007/011002	Mexico	03/05/2009
44	Food composition for functional foods and nutritional supplements	MX/A/2008/015295	Malaysia	13/05/2009
45	Composicion farmaceutica	2322911	Spain	01/07/2009
46	Food composition for functional foods and nutritional supplements	20100016246	U.S.A.	21/01/2010
47	Application of diosmin in manufacturing medicaments	101711768	China	26/05/2010
48	Pharmaceutical composition combining various venotonic and vasoprotective agents for the treatment of chronic venous insufficiency	2208498	European	21/07/2010
49	Externally-applied medicament composite for treating haemorrhoids	102641299	China	22/08/2012
50	Komposisi kombinasi, yang meliputi bahan aktif l-karnitin atau propionil l-karnitin, untuk pencegahan atau pengobatan insufisiensi vena kronis	2012/05320	Indonesia	27/12/2012
51	Dược phẩm chứa hoạt chất l-carnitin hoặc propionyl l-carnitin để phòng ngừa hoặc điều trị bệnh suy tĩnh mạch mạn tính	33254	Vietnam	25/04/2013
52	Суппозиторий ректальный коМбинированный препарат для лечения проктологических, урологических и гинекологических заболеваний "геМодан"	2012112648	Russia	10/10/2013

(*continued on next page*)

Table 6 (*continued*)

N°	Title	Code	Office	Publication date
53	Diosmin granules and preparation method thereof	103417493	China	04/12/2013
54	Composición farmacéutica que comprende la combinación de diversos agentes venotónicos y vasoprotectores para el tratamiento de la insuiciencia venosa crónica	2466318	Spain	10/06/2014
55	Composicion farmaceutica en forma de una suspension oral que comprende una fraccion flavonoica y goma de xantano	355719	Mexico	23/06/2014
56	Pharmaceutical composition in the form of an oral suspension including flavonoid fraction and xanthan gum	103877108	China	25/06/2014
57	Pharmaceutical composition in the form of an oral suspension including flavonoid fraction and xanthan gum	2745839	European	25/06/2014
58	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction and xanthan gum	WO/2014/096740	International	26/06/2014
59	Pharmaceutical composition in form of oral suspension containing flavonoid fraction and xanthan gum	1020140081738	Korea	01/07/2014
60	Pharmaceutical composition in the form of an oral suspension comprising a flavonoid fraction and xanthan gum	2013089255	Singapore	30/07/2014
61	Composição farmacẽutica na forma de uma suspensão oral compreendendo uma fração de flavonoide e uma goma de xantano	102013032405	Brazil	26/08/2014
62	Preparation for treating proctological, urological and gynaecological diseases	WO/2014/163520	International	09/10/2014
63	Pharmaceutical composition combining diosmin and hesperidin and its use in neuropathic pain	WO/2015/019334	International	12/02/2015
64	Combination composition, comprising as active ingredient L-carnitine or propionyl L-carnitine, for the prevention of treatment pf chronic venous insufficiency	53515	Serbia	27/02/2015
65	Suppositories for treating hemorrhoid, proctitis and other proctological inflammations	0002545994	Russia	10/04/2015
66	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	2929326	Canada	07/05/2015
67	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	WO/2015/065231	International	07/05/2015
68	Pharmaceutical composition in the form of an oral suspension including flavonoid fraction and xanthan gum	1/2013/000362	Philippines	22/06/2015
69	Komposisi farmasi dalam bentuk suspensi oral yang mengandung fraksi flavonoid dan gom xantan	2015/03820	Indonesia	28/08/2015
70	Diosmin tablet and preparing technology thereof	104906058	China	16/09/2015
71	Pharmaceutical composition as oral suspension including a flavonoid fraction and xanthan gum	130611	Romania	30/10/2015
72	Composition comprising melatonin and flavonoids for use in the treatment of tumors resistant to chemotherapy	WO/2016/009256	International	21/01/2016
73	Composition comprising melatonin and flavonoids for use in the treatment of tumors resistant to chemotherapy	2954585	Canada	21/01/2016
74	Pharmaceutical composition in form of oral suspension, which contains flavonoid fraction and xanthan gum	0002582954	Russia	27/04/2016
75	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	2013404117	Australia	16/06/2016
76	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	201627005331	India	22/07/2016
77	Medicinal composition with diosmin and application of medicinal composition with diosmin to biological medicines	105924442	China	07/09/2016
78	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	3064210	European	07/09/2016
79	Medicine composition containing iodized lecithin and preparation method thereof	105920060	China	07/09/2016
80	Composition for use in the treatment of tumors resistant to chemotherapy	2977910	Canada	09/09/2016
81	Composition for use in the treatment of tumors resistant to chemotherapy	WO/2016/139625	International	09/09/2016
82	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	105939719	China	14/09/2016
83	Agent in suppository form for treatment of haemorrhoids, proctitis and other inflammatory proctological disorders	20160271080	U.S.A.	22/09/2016
84	Composition comprising melatonin and flavonoids for use in the treatment of tumors resistant to chemotherapy	106535939	China	22/03/2017
85	Composition for preventing or treating hair loss or promoting hair growth or skin growth comprising diosmin as active ingredient	1017254610000*	Korea	10/04/2017
86	Composition comprising melatonin and flavonoids for use in the treatment of tumors resistant to chemotherapy	3169364	European	24/05/2017
87	Pharmaceutical composition in the form of an oral suspension including flavonoid fraction and xanthan gum	MY-1 60753-A	Malaysia	22/06/2017
88	Composition comprising melatonin and flavonoids for use in the treatment of tumor resistant to chemotherapy	20170209416	U.S.A.	27/07/2017
89	Composition for preventing or treating hair loss or promoting hair growth or skin growth comprising diosmin as active ingredient	WO/2017/116092	International	08/08/2017
90	Traditional chinese medicine extract composition for treating constipation as well as preparation method and application	107115351	China	01/09/2017
91	Composition for use in the treatment of tumors resistant to chemotherapy	201747032728	India	17/11/2017
92	A novel synergistic pharmaceutical formulation exhibiting anti-cancer activity	201741034218	India	17/11/2017
93	Composition for preventing or treating muscular disease containing diosmin or pharmaceutically acceptable salt thereof as active ingredient	1018093790000*	Korea	14/12/2017
94	Composition containing diosmin or salt thereof as active ingredient and having skin moisturizing improvement, skin exfoliation, skin elasticity enhancement, erythema inhibition, skin wrinkle alleviation, or skin photoaging retardation effect	WO/2017/213346	International	14/12/2017
95	Composition for use in the treatment of tumors resistant to chemotherapy	107530386	China	02/01/2018

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Table 6 (*continued*)

N°	Title	Code	Office	Publication date
96	Composition for use in the treatment of tumors resistant to chemotherapy	3265071	European	10/01/2018
97	Composición farmacéutica de diosmina y hesperidina y su uso en dolor neuropático	354614	Mexico	08/03/2018
98	Composition for use in the treatment of tumors resistant to chemotherapy	20180064774	U.S.A.	08/03/2018
99	Composition for preventing or treating muscle diseases, containing, as active ingredient, diosmin or pharmaceutically acceptable salt thereof	WO/2018/070705	International	19/04/2018
100	**A method of manufacturing a solution of nanoparticles of acetylsalicylic acid or diosmin or drotaverine**	**WO/2018/100413**	**International**	**07/06/2018**
101	Chinese and western medicine formula for treating haemorrhoids	108159242	China	15/06/2018
102	Composition for preventing or treating hair loss or promoting hair growth or skin growth comprising diosmin as active ingredient	108472307	China	31/08/2018
103	Medicinal composition containing diosmin sulfate derivatives and application thereof	108992456	China	14/12/2018
104	Method for treating skin diseases, burns, superficial and deep wounds	0002690945	Russia	16/04/2019
105	Combined soft dosage form of diosmin and troxerutin	0002689409	Russia	28/05/2019
106	Method for treating skin diseases, burns, superficial and deep wounds	0002691063	Russia	07/06/2019
107	Glycosylated flavonoid compound and preparation method and application thereof	110156855	China	23/08/2019
108	**A method of manufacturing a solution of nanoparticles of acetylsalicylic acid or diosmin or drotaverine**	**110372768**	**European**	**09/10/2019**
109	Combined soft dosage form for treating haemorrhoid diseases	0002705794	Russia	12/11/2019
110	Composition, method and kit for treatment of bacterial infections	WO/2019/226741	International	28/11/2019
111	Composition and method of treatment of bacterial infections	201841019182	India	29/11/2019
112	A composition for mitigating colitis and colorectal cancer	PI2018702227	Malaysia	06/12/2019
113	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid fraction	PI2021000084	Malaysia	20/01/2020
114	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	P/2021/0003	Jordan	20/01/2020
115	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	2019306315	Australia	23/01/2020
116	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	WO/2020/016408	International	23/01/2020
117	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	3106495	Canada	23/01/2020
118	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction and xanthan gum	3669879	European	24/06/2020
119	Application of diosmin and composition thereof in preparation of anti-obesity products	111544440	China	18/08/2020
120	Pharmaceutical composition in the form of an oral suspension comprising a flavonoid fraction and xanthan gum	P/2013/0355	Jordan	27/08/2020
121	Composition comprising melatonin and flavonoids for use in the treatment of tumors resistant to chemotherapy	201627044594	India	02/10/2020
122	Compound for regulating body weight imbalance, composition thereof and application thereof	WO/2020/224452	International	12/11/2020
123	Composition for use in preventing or alleviating dermatitis containing diosmin, and use thereof	1020200131071	Korea	23/11/2020
124	Composition for treating tumors resistant to chemotherapy and application of composition	112023053	China	04/12/2020
125	Compound for regulating body weight imbalance, composition thereof and application thereof	112188894	China	05/01/2021
126	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid fraction	771968	New Zealand	29/01/2021
127	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	20210023	Costa Rica	22/02/2021
128	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid fraction	11202100181Y	Singapore	25/02/2021
129	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	112423735	China	26/02/2021
130	Application of diosmin in alopecia prevention and hair growth	112494506	China	16/03/2021
131	Composicion farmaceutica en la forma de un comprimido masticable de diosmina o de una fraccion flavonoica	2021000763	Mexico	29/03/2021
132	Pharmaceutical composition in the form of an oral suspension including flavonoid fraction and xanthan gum	AP5563	African Regional Intellectual Property Organization	22/04/2021
133	Pharmaceutical composition in the form of an oral suspension including flavonoid fraction and xanthan gum	AP/P/2013/007323	Kenya	22/04/2021
134	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	1/077429	Vietnam	26/04/2021
135	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	3823588	European	26/05/2021
136	**Preparation method and application of diosmin derivative sustained release preparation**	**112843243**	**China**	**28/05/2021**
137	Composition for removing freckles, whitening skin and resisting inflammation and application thereof	112891242	China	04/06/2021
138	Composition comprising diosmin	WO/2021/123341	International	24/06/2021
139	**Microencapsulated formulation comprising diosmin, toxerutin and coumarins, composition thereof and use thereof for the treatment of circulatory disorders**	**3845222**	**European**	**07/07/2021**
140	Method of preparing tangerine charcoal cosmetic composition containing active components, cosmetic composition including tangerine charcoal, and tangerine charcoal mask pack	1020210084793	Korea	08/07/2021
141	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	1/2021/550037	Philippines	27/09/2021
142	Neue pharmazeutische orale zusammensetzung mit geringen nebenwirkungen enthaltend anti-tuberkulose arzneimittel	112011105169	Germany	04/11/2021
143	Mixture and composition for the prevention and treatment of diseases of the circulatory system and of related symptoms	WO/2021/229501	International	18/11/2021
144	Anticolon cancer drug - dinar: a combination of diosmin and naringenin and the process thereof	202011031417	India	28/01/2022
145	Compound for regulating body weight imbalance, composition thereof and application thereof	3949972	European	09/02/2022
146	Depigmenting dermopharmaceutical or cosmetic composition and use thereof	WO/2022/064083	International	31/03/2022
147	Compound for regulating body weight imbalance, composition thereof and application thereof	20220193104	U.S.A.	23/06/2022
148	**A method of manufacturing a solution of nanoparticles of acetylsalicylic acid or diosmin or drotaverine**	**3548001**	**Poland**	**11/07/2022**
149	Depigmenting dermopharmaceutical or cosmetic composition and use thereof	4035651	European	03/08/2022
150	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid fraction	0002811866	Russia	22/08/2022
151	Composition for preventing or treating proctological diseases	0002814279	Russia	12/10/2022
152	Diosmin cream and application	115624520	China	20/01/2023
153	Use of a new therapeutic combination to treat chronic venous insufficiency	WO/2023/021309	International	23/02/2023

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Table 6 (*continued*)

N°	Title	Code	Office	Publication date
154	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid moiety	P/2021/0003	Jordan	29/03/2023
155	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid fraction	10202300142P	Singapore	31/03/2023
156	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid fraction	P20237532B	Georgia	25/08/2023
157	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction comprising diosmin and xanthan gum	3669879	Lithuania	25/03/2024
158	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid fraction	MY-2 00586-A	Malaysia	27/03/2024
159	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction comprising diosmin, and xanthan gum	3669879	Portugal	04/04/2024
160	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction comprising diosmin and xanthan gum	65369	Serbia	30/04/2024
161	Co-amorphous solid forms of flavonoids	WO/2024/116042	International	06/06/2024
162	Use of a new therapeutic combination to treat chronic venous insufficiency	4387621	European	26/06/2024
163	Pharmaceutical composition in the form of a chewable tablet of diosmin or of a flavonoid fraction	812787	New Zealand	09/07/2024
164	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction comprising diosmin and xanthan gum	P20240550	Hungary	19/07/2024
165	Pharmaceutical composition in the form of an oral suspension including a flavonoid fraction comprising diosmin and xanthan gum	3669879	Poland	22/07/2024
166	Quy trình tổng hợp hệ nano phân hủy sinh học poly(axit lactic-co-glycolic) (plga) mang hỗn hợp thuốc diosmin và hesperidin, được phủ chitosan để điều trị suy giãn tĩnh mạch thông qua đường uống	103962	Vietnam	25/07/2024
167	Composition and application thereof in preparation of product with function of resting eye ageing	118384063	China	26/07/2024
168	Pharmaceutical composition in the form of an oral suspension comprising a flavonoid fraction and xanthan gum	E066379	Hungary	28/08/2024
169	Co-amorphous solid forms of flavonoids	20240285534	U.S.A.	29/08/2024
170	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	3823588	Lithuania	11/11/2024
171	Low-temperature cold-prepared high-activity skin microcirculation promoting composition and preparation thereof	118948663	China	15/11/2024
172	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid fraction comprising same	4473977	European	11/12/2024
173	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	EP3823588	Finland	27/12/2024
174	Farmaceutisk sammensætning i form af en tyggetablet af diosmin eller af en flavonoid del omfattende diosmin	3823588	Denmark	02/01/2025
175	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	66288	Serbia	31/01/2025
176	Quy trình tổng hợp hệ nano phân hủy sinh học poly(axit lactic-co-glycolic)/hydroxypropyl-β-xyclodextrin (plga/hpcd) mang thuốc diosmin, được phủ chitosan để sử dụng thông qua đường uống	109296	Vietnam	03/02/2025
177	Natural formulations to reduce cpd levels	WO/2025/034239	International	13/02/2025
178	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	P20250037	Croatia	14/03/2025
179	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	3823588	Poland	31/03/2025
180	Pharmaceutical composition in the form of a chewable tablet of diosmin or a flavonoid moiety comprising diosmin	E069700	Hungary	28/04/2025
181	Composition for preventing and treating neurodegenerative diseases and cognitive disorders	WO/2025/099614	International	15/05/2025
182	Pharmaceutical composition in form of chewable tablet of diosmin or flavonoid fraction	0002842242	Russia	24/06/2025
183	Use of a new therapeutic combination to treat chronic venous insufficiency	US20250332185	U.S.A.	30/10/2025
184	Pharmaceutical composition for treating TDP-43 proteinopathy, and preparation method therefor and use thereof	WO2026021621	International	29/01/2026

the European Patent Office (3845222 on the 07/07/2021). It regarded the development of microencapsulated formulation composed by a lipid, to be administered in the treatment of cardiocirculatory disorders as venous insufficiency, haemorrhoids, etc. The lipid employed in the formulation was preferably a phospholipoids, and the materials proposed were sunflower, corn or soy lecithin. The obtained carrier had a size lower than 400 nm and could be used as both medicament (preventing or treating) and cosmetic product.

4. Current challenges and future perspectives

Despite the great advantages offered by the use of DDS, some issues – both biological and technological/economical – still need to be addressed, in order to aim at clinical application [58], [59], [60].

Considering the biological issues, one of the first problems after DDS administration is the occurrence of clearance due to the recognition as foreign entities, thus opsonization and phagocytosis, but also the formation of a protein corona, could reduce the therapeutic activity; this issue could be reduced by adding biomimetic surface coatings. Another issue could be the biocompatibility of the nanocarriers, and particularly the long-term safety of the used material, especially when intended for chronic therapies. Both these situations could result in the occurrence of immune or inflammatory response, with a decrease in the efficacy of the system.

The achievement of the target site thus the reduced side effects, which are among the key strengths of DDS, are not always attainable. In fact, when using proteins or antibodies, the saturation of surface receptors is a limiting factor to their uptake, thus cell-penetrating peptides or other comparable compounds should be considered to increase cell permeation. Moreover, the presence of biological barriers continues to pose a challenge to the efficacy of drugs delivered using DDS. *In vivo* biodistribution studies or new *in vitro* biomimetic models, as organ-on-a-chip, could be employed to further explored these matters for the clinical application.

Finally, the translation of results from animals to humans is still challenging, since there are specificities in the physiology that could results in different outcomes: among them, gene expression, immunity and metabolism may differ. For this reason, new humanized animals

currently under development could represent more reliable preclinical models in assessing efficacy and safety.

From the technological/economical point of view, the scalability of the production methods is usually difficult; in fact, nanocarriers are generally obtained employing multi-step procedures which are difficult to scale up to continuous industrial manufacture. Moreover, several process parameters should be finely regulated to ensure the reproducibility of the platform, and features as size, surface and shape need to be monitored to ensure quality. Additionally, improving the shelf life of nanocarriers should be a major concern to ensure the commercialization. This complexity leads to higher production costs, which hinder industrial translation and, consequently, therapeutic accessibility. In fact, although the DDS market is projected to grow (110.13 billion USD expected in 2030 [60]), the economic impact of nanocarrier production represents one of the main constraints. To overcome these limitations, it is crucial to focus on industrial scale-up from the very earliest stages of development, from the selection of biocompatible and cost-effective raw materials to the establishment of simplified and replicable manufacturing processes. In this regard, the establishment of standardized protocols for the production and the safety evaluation for nanocarriers could help accelerate their approval by regulatory agencies.

Ultimately, it is important to implement the compliance with international Good Manufacturing and Clinical Practice (GMP and GCP) standards from the earliest stages of nanocarrier development, with the aim of facilitating an efficient industrial scale-up. Furthermore, collaboration between universities and industry can strengthen the quality of the dossiers submitted by including in-depth characterization studies as well as extensive clinical trials, thereby enhancing the overall prospects of regulatory approval.

Last but not least, the plethora of DDS published in literature and developed for diosmin delivery highlights that researchers' efforts have been focused on continuously designing new platforms, aimed at various routes of administration and for a wide range of therapeutic applications. Therefore, a critical comparison between them is extremely complicated, given that each research work supports its own hypotheses with relevant and valuable evidence. At this point, what emerges is the need to focus research efforts on overcoming the aforementioned challenges to ensure that clinical translation and market authorization become the primary goals to contribute significantly to current therapies. With particular regard to diosmin administration, the commercialization of drug delivery platforms could be a key element for overcoming the molecular limitations of this compound and for exploiting its multiple therapeutic capabilities.

5. Conclusions

The present review was meant to provide an overview of diosmin, from its properties to commercialization.

Although this drug has raised interest for several pharmacological activities, there are severe limitations to its use, which justify the molecule poor presence on the market. Such limitations are related to diosmin molecular structure, and results in low bioavailability after oral administration. In fact, commercially available products containing diosmin (which are generally tablets) are produced in high doses to compensate the poor drug bioavailability. Since this approach increases the risk of occurring side effects, other strategies are required, and the employment of drug delivery systems for diosmin encapsulation could be successful in increasing its bioavailability. For this reason, the analysis of literature provides an overview of the nanocarriers developed to deliver diosmin, focusing on their technological characteristics, in terms of raw materials and preparation procedures, as well as carrier size, superficial charge, morphology, diosmin encapsulation efficiency, and drug release profile. This information is beneficial for understanding the findings from *in vitro* and *in vivo* studies and the evidence reported in these research publications. The limited number of publications and the results confirming the advantages of diosmin encapsulation in drug delivery systems should encourage the readers to further explore this research, directing it towards other routes of administration that could be exploited considering the variety of therapeutic properties of the molecule, with the aim of maximizing the diosmin achievement of the target site. Finally, in the last paragraph the presence of very few patents regarding diosmin encapsulated in DDS emphasizes again the gap in the research, and consequently suggests that these research efforts might also meet the demands of pharmaceutical companies, thus opening new significant research opportunities in the field, ensuring patient well-being through the use of this natural compound.

CRediT authorship contribution statement

Cinzia Cimino: Conceptualization, Investigation, Project administration, Writing – original draft. **Angela Bonaccorso:** Writing – original draft, Writing – review & editing. **Teresa Musumeci:** Writing – review & editing. **Claudia Carbone:** Project administration, Writing – review & editing. **Rosario Pignatello:** Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
AChE	Acetylcholinesterase
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Aldose reductase
ARPE-19	Human retinal pigment epithelial cell line
AST	Aspartate aminotransferase
Bax	Bcl-2-associated X protein
Bcl-2	B cell lymphoma-2
BCS	Biopharmaceutics classification system
CAT	Catalase
cGMP	Cyclic guanosine monophosphate
CK	Creatine kinase
CK-MB	MB isoenzyme
COX-2	Cyclooxygenase
CS	Chitosan
cTcT	Cardiac troponin T
DDS	Drug delivery systems
DPPH	2,2-diphenyl-1-picrylhydrazyl
EE%	Encapsulation efficiency %
FDA	Food and drug administration
FGF2	Fibroblast growth factor 2
GE	Gelatin
GGT	Gamma glutamyl transferase
GPx	Glutathione peroxidase
GR	Glutathione reductase

GSH	Glutathione
GST	Glutathione-S-transferase
HDF	Normal human dermal fibroblasts
HepG2	Human hepatocellular cells
HEWL	Hen egg white lysozyme
HL-60	Human promyelocytic leukemia
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropylmethyl-cellulose
HPS	Hydroxypropyl starch
HPβCD	2-hydroxypropyl-β-cyclodextrin
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
ITT	Insulin tolerance test
JNK	c-Jun N-Terminal kinase
Keap-1	Kelch-like ECH-associated protein 1
LDH	Lactate dehydrogenase
MC	Methyl cellulose
MDA	Malondialdehyde
MIC	Minimum inhibitory concentration
MMP-9	Matrix metalloproteinase-9
MW	Molecular weight
NF-κB	Nuclear factor-kappa B
nHAp	Nanohydroxyapatite
NLC	Nanostructured lipid carrier
NO	Nitric oxide
NP	Nanoparticles
NRF2	Nuclear factor erythroid 2-related factor 2
OGTT	Oral glucose tolerance
p38-MAPK	p38 mitogen-activated protein kinases
PASI	Psoriasis area severity index
PC	Phosphatidylcholine
PCT	Patent cooperation treaty
PDI	Polydispersity index
PEG 6000	Polyethylene glycol 6000
PEO	Polyethylenoxide
PLGA	Poly(D,L-lactide-co-glycolide)
PLX188	Poloxamer 188
PVA	Polyvinyl alcohol
RPECs	Retinal pigment epithelial cells
SA	Sodium alginate
SD	Sprague-Dawley
SLN	Solid lipid nanoparticles
SOD	Superoxide dismutase
STPP	Sodium tripolyphosphate
TB	Total bilirubin
TC	Total cholesterol
TEM	Transmission electron microscopy
TMC	Trimethyl chitosan
TNF-α	Tumor necrosis factor
TPP	Tripolyphosphate
TRPV1	Transient receptor potential vanilloid 1
VEGF-AZ	Vascular endothelial growth factor A
VEGF-C	Vascular endothelial growth factor C
ZP	Zeta potential

Data availability

No data was used for the research described in the article.

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