4open 2023, **6**, 9

https://doi.org/10.1051/fopen/2024002

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REVIEW ARTICLE OPEN ACCESS

# Review of commercially available nano-drugs and nano-delivery systems: challenges and perspectives

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Received 13 January 2024, Accepted 7 August 2024

**Abstract –** Nano-drugs and nano-delivery systems are rapidly evolving, with new strategies emerging in the current practices. The evolution of these technologies began with modifying the chemical structure, progressing to supramolecular ionic complexes, and culminating in elegant *ad hoc* delivery systems. Nanoparticles have numerous benefits as a carrier system for delivering therapeutic agents to intra-arterial sites. These benefits include their subcellular size, targeted surfaces, good suspensibility, and uniform dispersity, making them an ideal choice for catheter-based delivery. Despite the advancements made in the field of nano-drugs and nano-delivery systems, there are still some hurdles to overcome in terms of their commercial availability. The current review presents an updated summary of recent advancements in nano-drugs and nano-delivery systems, including their commercial availability. We aim to discuss the present challenges and prospects of commercially available nano-drugs and nano-delivery systems. Here, we provide a precise and informative overview of the current state of these technologies and underscore the potential they hold for future developments. Further, we have categorized commercially available modifications, name, parent company and their main applications in nano-drugs.

**Keywords:** Nano-drugs, Nanoparticle, Delivery system, Vaccine, Liposome, Exosome, Stealth effect, SLN, Inclusion and dispersion systems, Solid state reactive mixing, Nanosome, Drug carrier

## Highlights

1. Historical development of novel formulation to enhance solubility and bioavailability too.
2. Enlisting the several chemical strategies available to date: From delivery to nano-drugs.
3. Alternative and non-canonical delivery technologies.
4. Importance of immunogenicity response in the host: Stealth effects.

## Introduction

Delivery technologies have improved patient health through novel drugs and advanced formulations. Drug delivery technologies are platforms that enable the conversion of potential and/or poor soluble active pharmaceutical ingredients (APIs) into successful therapies. They are naturally occurring nutrients or food ingredients that have been shown to have medical and health benefits in disease prevention and treatment [1]. Nutraceuticals are relatively more biocompatible and cost-effective options than synthetic drugs. They show a higher public acceptance as the general public starts to illustrate increased interest in and consciousness of healthy living. Nutraceuticals, in particular, have gained increased commercial and scientific attention. The market size of nutraceuticals has grown significantly, primarily due to the health benefits they offer. A report by Statista Estimates, Grand View Research, indicates that the US nutraceutical market was worth over 71 billion dollars in 2017 and is estimated to reach over 133 billion dollars by 2025 [2].

## Historical background

Since the 1960s, nanotechnology has garnered significant attention among pharmaceutical scientists due to its potential in drug delivery [3]. One of the earliest examples of this was the introduction of liposomes in 1965, which rapidly became a popular method of drug delivery [4].

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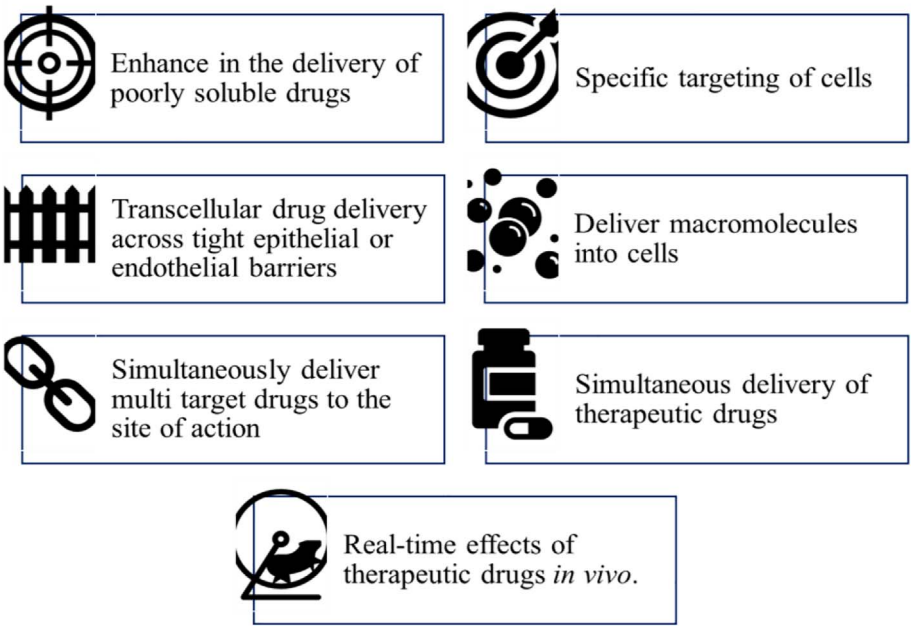


**Figure 1.** The importance of nano-drug and nano-delivery.

Subsequently, in 1978, an article was published demonstrating the use of nanoparticles as drug carriers [5]. In essence, nanotechnology refers to the ability to produce and manipulate materials or objects at the nanoscale level. These drug delivery systems, with particle sizes in the nanometer range, are commonly referred to as nano-drug delivery systems. The development of such systems has become a routine technology for studying the activity of drugs both in vivo and in vitro. They prove particularly useful when faced with challenges such as large molecular weight, poor stability, difficult absorption, or the need for targeted or controlled release of drugs. As such, nano-drug delivery systems serve as one of the most promising solutions to these challenges, as shown in Figure 1.

Despite their vast potential benefit, a large number of nutraceuticals are hydrophobic (poorly water-soluble), resulting in poor bioavailability when taken in their "pure" form. This challenge is not limited to the nutraceutical industry, as it is estimated that 90% of preclinical small-molecule drug candidates are poorly water-soluble too [6]. While an accurate definition of bioavailability defers slightly between different sources and fields, it generally refers to the extent to which an administered drug, nutrient, or substance is absorbed and used by its intended target in the body. It is thus essential to maximize the bioavailability of any pharmaceutical or nutraceutical of interest to ensure maximum benefit and efficacy. Increasing the administered dose in order to increase the amount of absorbed drug to a therapeutic concentration seems like a simple solution. Furthermore, this approach is not recommended as it involves numerous complications in terms of the feasibility of administering such a large dose, potential side effects such as toxicity and immunogenicity, and the monetary and environmental cost of wasted material (Table 1).

Numerous approaches have been taken to improve the bioavailability of insoluble drugs and nutrients [6, 7]. These approaches generally fall under three strategies:

1. Modifications of the chemical or physical properties of the drug;
2. Mixing with co-ingredients or co-solvents;
3. Development of drug carrier systems that improve the interactions between the drug and surrounding biological molecules, tissues and cells.

The latest drug delivery biotechnologies employ various strategies to improve drug solubility, circulation time, penetration, absorption, targeted activity, and off-target accumulation [8]. These biotechnologies aim to enhance patient tolerability and acceptance, ultimately leading to better treatment outcomes. Transdermal delivery (TDD) systems have become an increasingly popular drug delivery option due to their non-invasive nature and ability to bypass the gastrointestinal tract. These systems utilize biodegradable microneedle patches that are composed of materials such as polylactic acid and hyaluronic acid [9]. These microneedles have been designed to be minimally invasive and painless, penetrating only the outermost layer of the skin to increase drug permeability. After use, the microneedle patches dissolve and leave no sharp waste, making them a safe and eco-friendly drug delivery option.

Nano-drugs have emerged as a promising avenue in the treatment of chronic human diseases and in targeted delivery of medicines. Despite the potential benefits, there is limited knowledge regarding their commercial availability and associated challenges. In this review, we present a synthesis of challenges and perspectives in commercially available nano-drugs and nano-delivery systems. Our aim is to bridge the gap between academic studies and industrial

**Table 1.** Recent commercially available modifications and their main applications in nano-drugs and delivery systems.

| Type of modification | Name$^{TM/®}$ | Parent company | Main application | Reference |
|---|---|---|---|---|
| Chemical moiety | Norvir | Abbvie | Antiviral | [11] |
| Chemical moiety | Losentic | Novartis | Antihypertensive | [12] |
| Chemical moiety | Vasotec | Merck | Antihypertensive | [12] |
| Chemical moiety | Ceftin | GSK | Antibiotic | [13] |
| Chemical moiety | Cipro IV | Merck | Antibiotic | [16] |
| Supramolecular | BioPerine | Sabina Corp | Blood Sugar Lower | [17] |
| Supramolecular | Taxol | BMS | Antineoplastic | [20] |
| Supramolecular | Taxotere | Sanofi | Antineoplastic | [21] |
| Micelle/Emulsion | MyCell | Glow Life Tech | Lipophilic Drug Carrier | [22] |
| Micelle/Emulsion | Curepods | Cure Pharma | Lipophilic Drug Carrier | [23] |
| Micelle/Emulsion | uGOO | EmbarkoNano | Lipophilic Drug Carrier | [26] |
| Liposome | Cyclosome | Hi-Tech Pharma | Lipophilic Drug Carrier | [27] |
| Liposome | Phytosome | Indesa | Lipophilic Drug Carrier | [34] |
| Polymeric Nanoparticle | Genexol | Samyang | Antineoplastic | [35] |
| Nano Solid Dispersion | Sporanox | Janseen Pharma | Antifungal | [37] |
| Nano Solid Dispersion | Nimotop | Bayer | Antihypertensive | [38] |
| Inclusion Complex | Fenumat | Akay Ingredients | Lipophilic Drug Carrier | [44] |
| Inclusion Complex | CyLoc | Tesseract Medical Research | Cyclodextrin Cages as a Carrier | [45] |
| Inclusion Complex | SSRM | Folium Labs Corp | HA Dispersion as a Carrier | [52] |

availabilities. We have categorized commercially available nano-drugs based on their modifications, name, parent company, and applications. Our review provides a concrete framework for academia and industry to enhance their understanding of commercially available nano-drugs and their potential applications. By consolidating and presenting the latest research on the topic, we hope to contribute to the literature gap and facilitate further advancements in this field.

## Drug modification

Drug modification is a process that entails chemical and physical alterations to improve the interaction between drugs and their microenvironment. One of the primary objectives of drug modification is to enhance the water solubility of drugs [10]. By modifying the chemical structure of drugs and/or their physical properties, drug modification aims to make them more compatible with the microenvironment. The ultimate goal is to optimize the efficacy and safety of drugs, thereby improving patient outcomes. The solubility and absorption of a drug can be significantly improved by chemically altering the existing functional groups of the drug. For example, ritonavir (Norvir by Abbvie, Inc), a critical protease inhibitor for HIV, is modified by a thiazole moieties to improve its water solubility and metabolic stability [11]. Another approach is the synthesis of prodrugs, most commonly alkyl ester prodrugs such as the angiotensin-converting-enzyme inhibitors benazepril (Lotensin by Novartis Pharmaceuticals, Inc) and enalapril (Vasotec by Merck) [12]. The ester prodrugs have been used in pharmaceutical formulations for a long time, which give them improved solubility and penetration of the new structure that is a non-active precursor. This prodrug undergoes in vivo chemical or enzymatic cleavage of the ester group upon there uptake and generate the active drug. Although chemical modifications can serve as a versatile tool, it can be extremely challenging and resource exhausting to achieve for some specific APIs. Chemical modifications might include challenging synthetic routes, where the product (if obtained) must undergo extensive pre-clinical and clinical characterization and testing to ensure the desired therapeutic and chemical properties are obtained. This means that any new product will be subjected to extensive regulatory considerations.

Modifications to the physical properties of the drug may circumvent the above-mentioned synthetic and regulatory challenges of chemical modifications. "Physical" modifications primarily target the crystal form of the drug. When a drug possesses a stable crystal form, it can be an extremely challenging task to break those strong intermolecular interactions in order to solubilize it. Disordered, amorphous packing, on the other hand, renders the drug more water-soluble [13]. One case example is Ceftin by GSK, an amorphous form of the antibiotic cefuroxime which is completely insoluble in water in its original form [14]. Because the solubility of amorphous forms depends on the reduced molecular-packing stability of the latter, they can be very challenging to form and stabilize. Therefore, they are often protected by multiple patents which prevent early generic entry.

## Co-ingredients and co-solvents

Another strategy to improve the bioavailability of insoluble drugs and nutraceuticals is by addition of a co-ingredient or co-solvent that improves its solubility and penetration. One of the main co-ingredient strategies is the addition of pH modifiers, which can alter the pH of the drug's local environment into one in which the drug is in an ionic and more soluble form [15]. A classic example is the antibiotic Ciprofloxacin (Cipro IV), which is poorly

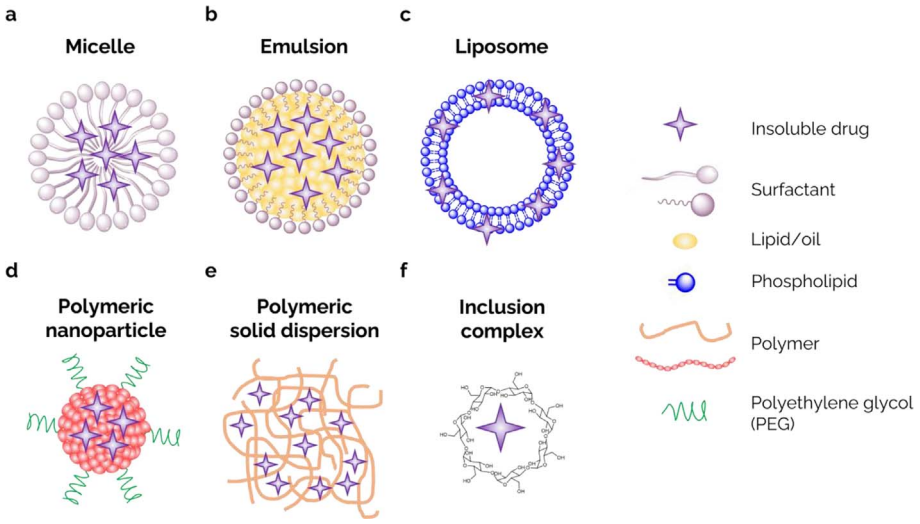


**Figure 2.** Drug carrier systems of poorly water-soluble drugs for (a) lipid or surfactant-based micelles, (b) mico- and nanoemulsions, (c) phospholipid-based liposomes, (d) PEGylated polymeric nanoparticles, (e) polymer-based solid dispersions, and (f) cyclodextrin-based inclusion complexes.

soluble in water alone, but is formulated with hydrochloric acid and lactic acid for improved solubility [16]. This approach, however, relies on the ionizability (acidity) of the drug, and the compatibility between its optimal solubility pH range and physiological pH.

The bioavailability of nutraceuticals can be further improved by the addition of excipients (co-ingredients) that act as penetration enhancers. In fact, many penetration enhancers can be found in natural sources, and are often plant extracts, alkaloids and flavonoids such as piperine and quercitin, with well studied mechanisms of actions [17]. BioPerine® is a patented standardized piperine extract by Sabinsa Corporation that has been shown to increase the bioavailability of certain nutraceuticals. Other natural ingredients, such as (*Piper nigrum* L.), long pepper (*Piper longum* L.), and ginger (*Zingiber officinalis* L.) have also been shown to increase the bioavailability of drugs, though their mechanism of action is not well-known [18]. Non-herbal penetration enhancers include fatty acids, alcohols and cholates, which often decrease the barrier effect of cells by disrupting the lipid arrangements between them [19]. Zemvelo by Mineralife Nutraceuticals relies on the addition of fulvic acid in its formulations to promote the absorption and bioavailability of delivered nutrients and minerals.

Formulation of drugs with co-solvents is also a commonly used practice. It involves increasing drug solubility and penetration by addition of co-solvents such as alcohol, polymers, and biomolecules that solubilize non-polar drugs, but require the addition of surfactants to prevent precipitation upon dilution in biological fluid. Chemotherapy drugs paclitaxel and docetaxel have been commonly formulated using the co-solvent approach, their most common formulations being Taxol (by Bristol-Myers Squibb) and Taxotere (Sanofi-Aventis), respectively [20]. Both these formulations however lead to hypersensitivity reactions from the surfactants used. As a result, newer co-solvent formulations use polyethylene glycol (PEG) as co-solvent and Tween 80 as surfactant, which have reported better patient tolerance and less adverse effects compared to the solvents and surfactants used in older formulations [21]. However, the co-solvency method still presents some disadvantages, such as uncontrolled precipitation of the drug upon its interaction with biological fluid, and potential decrease in the stability and effectiveness of the drug [6].

## Drug carrier systems

Development of drug carrier systems is the most recurrent strategy to improve the bioavailability of insoluble drugs, as illustrated in Figure 1. Carrier systems serve as an interface that facilitates the interactions between the pharmaceuticals and their microenvironment, mainly by increasing solubility, penetration, circulation time, and offering potential targeting benefits. Glow LifeTech, for example, relies on the formation of micelles through their plant based MyCell™ Technology to increase the water solubility of fat-soluble nutraceuticals, as it is shown in Figure 2a. Most drug carrier technologies fall under one of two categories: lipid-based or polymer-based drug delivery systems.

Lipid-based drug delivery technologies involve the use of emulsions, micelles, liposomes and pro-liposomes, or solid-lipid nanoparticles (SLN) to enhance the solubility of APIs and their delivery to the target site. Products such as CURE-Epods™ and CUREdrops™ from CURE Pharmaceuticals rely on a range of lipid-based drug delivery technologies [22, 23].

Micro- and nano-emulsions have seen increased use in drug delivery technologies. In fact, these suvramolecular structures are composed of a thermodynamically stable mixture of oil/lipid, water, surfactants and co-surfactants, and the APIs itself, all together forming a stable heterogenous system compared to conventional emulsions as drawn in Figure 2b. SōRSE Technology, Industrial Sonomechanics,

and VESIsorb®, for example, rely on the formation of stable nanoemulsions for the improved delivery of nutraceuticals like hemp extracts and cannabidiols [24]. Perhaps the most attractive type of micro-emulsions is self-micro-emulsifying drug delivery systems (SMEDDS). Self-emulsifying formulations involve an isotropic mixture of oil/lipid, surfactants and APIs (without water), which spontaneously emulsifies upon ingestion and interaction with gastro-intestinal fluid, resulting in droplets smaller that 250 nm in size. $\mu$GOO by EmbarkNano is marketed as a nanoemulsion "precursor" to be used to generate their other products such as $\mu$SHOT nanoemulsions and $\mu$CREAM "nano topical". Lipid based micro-emulsions, such as Vitalipid by Kabi, O2W by Micellae Delivery Systems, and SureNano™ have been frequently used for the enhanced delivery of nutraceuticals [25–27]. As higher surface area of nanoparticles results in their faster absorption, micro-emulsions often require the addition of a large concentration of surfactants in order to reduce their size and increase their surface area-to-volume ratio. This presents the major drawback of self-micro-emulsifying delivery technologies, and emulsion technologies overall, as large concentrations of surfactants may result in a decrease of the drug encapsulation ability of the micro-emulsions due to increase hydrophilicity of the matrix, which may lead to the precipitation of the drug upon dilution in physiological fluid [28]. Additionally, the utilization of large concentrations of surfactants has been shown to lead to patient hypersensitivity and low tolerance [29].

Liposomes represent a type of lipid-based drug delivery technology that circumvents the need for surfactants. These spherical nanoparticles are composed of phospholipid bilayers and have been employed as a promising candidate in the field of drug delivery. They contain an aqueous center that is entrapped by a hydrophobic lipid bilayer shell as shown in Figure 2c. Liposomes can thus be great carriers of both hydrophobic and hydrophilic compounds. Hi-Tech Pharmaceuticals, for example, uses their Cyclosomes™ technology to entrap hydrophobic compounds inside cyclodextrins and deliver them using a liposome carrier. Quicksilver liposomal Delivery Systems® by Quicksilver Scientific also relies on high-phosphatidylcholine phospholipid mixes to produce stable small delivery vehicles, whereas Indena S.p.A. relies on natural lecithin phospholipids in their Phytosome® drug delivery system [30]. Liposomes are often formulated with the addition of PEG for additional water solubility and non-immunogenicity, as PEG helps reduce their detection and clearance. Liposomes can further be functionalized by targeting moieties to provide site-specific activity. Perhaps the most relevant examples of the use of liposomes as carrier systems are the mRNA based COVID-19 vaccines, such as the ones developed by Moderna and Pfizer/BioNTech [31]. Moreover, the first FDA-approved nanoparticle therapeutic was PEGylated liposomal doxorubicin (Doxil by Sequus Pharmaceutical, Inc.) [32]. One major drawback of liposomes is their reduced shelf-life and long-term stability, and potential leakage of the entrapped drug over time. A solution to that was the introduction of pro-liposomes, a dry mixture of powder lipid, drug, and other ingredients that form multilamellar vesicles (liposomes containing liposomes) upon their hydration right before drug administration or upon reaction with physiological fluid in vivo.

Polymer-based drug delivery technologies offer the same advantages as lipid-based technologies (enhanced bioavailability of drugs, site-targeting), with the added benefits of ease of functionalization and higher stability. Polymer-based technologies typically involve liquid formulations of polymeric micelles/nanoparticles, or solid formulations of solid dispersions and co-crystals.

Polymeric micelles are nanoparticles that encapsulate hydrophobic drugs and nutraceuticals as a result of hydrophobic-hydrophilic interactions. To ensure both a hydrophobic environment for the drug as well as solubility in aqueous solutions, the nanoparticles are formed of bi-block of tri-block copolymers, polymers that contain both hydrophobic and hydrophilic blocks, as shown in Figure 2d. The polymeric micelles have low critical micellar concentrations, meaning they maintain their stability and form even at low polymer concentrations. They also provide improved solubilization, stability, and patient tolerability compared to micelles formed with hydrophilic surfactants. Genexol-PM by Samyang, a polymeric nanoparticle containing paclitaxel, reported better safety and fewer side effects compared to its earlier formulations relying on co-solvency with ethanol and cremophore EL [33]. The hydrophobic block of the polymer is often made of PEG, which increases the circulation time of the nanoparticles by making them less likely to be cleared by the reticuloendothelial system. However, it has been reported recently that pre-existing anti-PEG antibodies can lead to the quick clearance of PEG-containing nanoparticles, with an increased risk of immunogenicity and adverse events [34, 35].

Solid formulations relying on the formations of solid dispersions and co-crystals have been successful at increasing the bioavailability of drugs as well as generating commercial success to the manufacturer [6]. Solid dispersions are often formed from a polymer "solvent" such as PEG, polyvinyl pyrrolidone (PVP), or HPMC (a cellulose derivative) with interspersed drug withing the polymer, either in as amorphous form or as a molecular dispersion within the polymer matrix, as illustrated in Figure 2e. Solid dispersions increase the solubility of drugs by preventing the packing of the drug into a stable crystalline form and/or due to an increase in hydrotrophy behavior by forming a molecular adduct [36]. Multiple formulations involving solid dispersions have shown a considerable increase in drug solubility, such as Sporanox by Janssen Pharmaceuticals [37], a solid dispersion of the antifungal itraconazole in HPMC, or Nimotop by Bayer Ltd [38], a solid dispersion of the calcium channel blocker nimodipine in PEG. Despite their benefits, solid dispersion is the most commonly formed by hot melt extrusion, a very energy-exhaustive technique. Other formation techniques include spray-layer, which requires the presence of an additional substrate onto which the polymer and drug are deposited [39, 40].

One derivative of the solid dispersion method that has seen increased application is the formation of "inclusion complexes". Inclusion complexes rely on a similar

mechanism to molecular solid dispersions in that they form "host-guest" complexes where drugs are held inside matrix cavities by intermolecular interactions such as van der Waals interactions and hydrogen bonding. Inclusion complexes have been formed from natural biomolecules such as fenugreek fibers and starch [41, 42], synthetic cyclic oligomers like calixarenes [43], and poly- and oligosaccharides like arabinogalactan, glycyrrhizin, and cyclodextrins [44]. FENUMAT™ by Akay Natural Ingredients Private Limited is based on the complexation of active ingredients in fenugreek fiber matrix to enhance the bioavailability of phytonutrients. Natural and synthetic cyclodextrins (CDs) are by far the most commonly used "host" molecules in inclusion complexes for drug delivery applications. CDs have a truncated cone structure, with a hollow hydrophobic interior and a hydrophilic exterior, which provides a good environment to trap hydrophobic drugs and solubilize them in aqueous media, as shown in Figure 2f. The first FDA approved cyclodextrin-containing drug product was Sopranox oral and IV solution by Janssen Pharmaceuticals, which contained itraconazole entrapped in a synthetic CD [45]. Tesseract Medical Research uses their proprietary CyLoc™ and DexKey™ technologies to entrap and then release active ingredients from cyclodextrin cages. These CDs inclusion complexes are typically formed by freeze-drying, spray-drying, kneading or co-precipitation [45–48].

This mini-review was not meant to discuss the all theoretically and commercially available portfolio of delivery systems; however, it is reported the following definition of dendrimers and nano-gels, since the pivotal impact that these structures are showing in the pharmaceutical space.

### Dendrimer

Dendrimers are hyperbranched nanocarriers formed by a central core, branching monomers, and functionalized peripheral groups. Dendrimers synthesis can start from the core elements (divergent polymerization) or from the peripheral branching units (convergent polymerization), resulting in a structure with a hydrophilic surface and a hydrophobic central core. Molecules can be transported by dendrimers either incorporated in the core and branches, either conjugated to the terminal group [49].

### Nano-gel

Nanogels are three-dimensional hydrogel materials in the nanoscale size range formed by cross-linked swellable polymer networks with a high capacity to hold water, without actually dissolving into the actually dissolving into the aqueous medium [50, 51].

## Alternative and non-canonical delivery technology

A novel formulation in delivery systems is broke out by Folium Labs. This delivery system consists of proprietary solid-state reactive mixing (SSRM) technology that relies on encapsulating active ingredients and nutrients with hyaluronic acid (HA) matrices [52, 53].

HA is a naturally occurring polysaccharide and a primary constituent of extracellular matrices. Given its biocompatibility, biodegradability, and natural presence within the human body, HA is a superb matrix for forming inclusion complexes. Additionally, its remarkable mucoadhesive properties make it an excellent carrier for buccal and sublingual drug delivery [19]. HA and its derivatives have been widely used as carriers of multiple classes of drugs and active molecules (nucleic acids, peptides and proteins, chemotherapeutics, imaging agents, and photosensitizers) in multiple drug delivery technologies (nanoparticles, micelles, hydrogels, emulsions, films) [54–56].

HA has specific receptors expressed on cell surfaces that mediate its absorption into cells (endocytosis). These receptors are present in high concentrations in joint tissue (articular cartilage) and fluid (synovial fluid). They are overexpressed by tumors [54, 55], making HA an ideal carrier to deliver anti-inflammatories and chemotherapeutics with little to no synthetic alteration required for targeted delivery. Moreover, the functional groups (carboxyl and hydroxyl groups) present on HA enable its easy functionalization with bonds that are signal-responsive and break upon encountering specific chemical or physical cues such as pH, light, or molecules that are over expressed in tumor environments, enabling not only targeted tumor delivery, but also triggered release of the drug/nutraceutical of interest [56]. SSRM technology involves a solvent-free, low-energy, green, one-step complexation process. The drugs, nutrients, and matrix used are all commercially available, making SSRM a very low-cost technology. The active ingredients are held within the HA matrix by hydrogen-bonding and van der Waals interactions and do not rely on any specific interactions between the drug and HA, making SSRM an easily scalable and translatable technology to use with a wide range of hydrophobic drugs and nutraceuticals. Moreover, the fact that SSRM is not a nanotechnology, nor does it rely on chemical modifications to the drug or natural HA makes it easier and faster to meet regulatory compliance and bring the products to market.

Proof-of-concept animal studies on a number of nutraceuticals formulated using SSRM have shown a significantly increased bioavailability by up to 10 times depending on the ingredient studies [57, 58].

The first use of HAs in nanotechnology for delivery systems date back to early 2010s. The introduction of HAs follows the need for the stealth effect of nanoparticles that have been introduced in the previous years via conjugations of high hydrophilic proteins with several kinds of combination: HPMA/PEG/PLA/PLGA [59].

## Stealth effect

The meaning of "stealth effect" and/or "pseudo stealth effect" refers to the different observed in the pharmacokinetics of the delivery systems [60]. The first thing to the mind

about these novel formulations is the "invisibility" of the nanoparticles in the body that is reflected in a major "longevity" of the nanoparticles in the blood, giving to these delivery systems a much bigger chance to reach out to the target tissue, since they are not captured by the macrophage (or other native immunity alert). Another characteristic of nanoparticles with stealth effect is that they are considered bio-inspired and bio-mimetics to cellular membranes, such as extracellular vesicles (exosomes) [61–64].

## Conclusion

Nano-drugs have emerged as a promising avenue in the treatment of chronic human diseases, offering several advantages such as targeted drug delivery, enhanced bioavailability, and improved pharmacokinetics. However, despite their potential, there is a lack of information on their commercial availability and numerous challenges associated with their development and delivery.

In this comprehensive review, we have analyzed the latest research and experimental findings and commercially available nano-drugs and nano-delivery systems. We have categorized the commercially available nano-drugs based on their type, including liposomes, nanoparticles, dendrimers, and others. Furthermore, we have discussed the challenges associated with nano-drug development, including toxicity, stability, and scale-up issues. We have also highlighted the regulatory hurdles and patent-related challenges that need to be addressed to facilitate the translation of nano-drug research into clinically viable products. Overall, this review provides a comprehensive and detailed overview of the current state of commercially available nano-drugs and nano-delivery systems to make a concrete bridge in the industry and academy.

### Conflicts of interest

All the authors declare no conflicts of interest.

### Ethics approval

Ethical approval was not required.

### References


1. DeFelice SL (1995), The nutraceutical revolution: Its impact on food industry R&D. Trends Food Sci Technol 6, 2, 59–61.
2. Fuoco D (2015), Hypothesis for changing models: current pharmaceutical paradigms, trends and approaches in drug discovery. PeerJ PrePrint e813v1.
3. Feynman RP (1960), There's plenty of room at the bottom. Eng Sci 23, 5, 22–36.
4. Bangham AD (1993), Liposomes: the Babraham connection. Chem Phys Lipids 64, 1–3, 275–285.
5. Widder KJ, Senyei AE, Scarpelli DG (1978), Magnetic microspheres: a model system for site specific drug delivery in vivo. Proc Soc Exp Biol Med 158, 2, 141–146.
6. Kalepu S, Nekkanti V (2015), Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B 5, 5, 442–453.
7. Vargason AM, Anselmo AC, Mitragotri S (2021), The evolution of commercial drug delivery technologies. Nat Biomed Eng 5, 9, 951–967.
8. Merkus FW, Verhoef JC, Marttin E, Romeijn SG, van der Kuy PH, Hermens WA, Schipper NG (1999), Cyclodextrins in nasal drug delivery. Adv Drug Deliv Rev 36, 1, 41–57.
9. Kim JH, Shin JU, Kim SH, Noh JY, Kim HR, Lee J, Chu H, Jeong KY, Park KH, Kim JD, Kim HK, Jeong DH, Yong TS, Park JW, Lee KH (2018), Successful transdermal allergen delivery and allergen-specific immunotherapy using biodegradable microneedle patches. Biomaterials 150, 38–48.
10. Thornber CW (1979), Isosterism and molecular modification in drug design. Chem Soc Rev 8, 4, 563–580.
11. Kempf DJ, Sham HL, Marsh KC, Flentge CA, Betebenner D, Green BE, McDonald E, Vasavanonda S, Saldivar A, Wideburg NE, Kati WM, Ruiz L, Zhao C, Fino L, Patterson J, Molla A, Plattner JJ, Norbeck DW (1998), Discovery of ritonavir, a potent inhibitor of HIV protease with high oral bioavailability and clinical efficacy. J Med Chem 41, 4, 602–617.
12. Beaumont K, Webster R, Gardner I, Dack K (2003), Design of ester prodrugs to enhance oral absorption of poorly permeable compounds: challenges to the discovery scientist. Curr Drug Metab 4, 6, 461–485.
13. Laitinen R, Löbmann K, Strachan CJ, Grohganz H, Rades T (2013), Emerging trends in the stabilization of amorphous drugs. Int J Pharm 453, 1, 65–79.
14. Fuchs T (2007), Case study: Cefuroxime axetil: an oral prodrug of cefuroxime, in: V.J. Stella, R.T. Borchardt, M.J. Hageman, R. Oliyai, H. Maag, J.W. Tilley (Eds.), Prodrugs. Biotechnology: pharmaceutical aspects, vol. V, Springer, New York, NY, pp. 1195–1205. https://doi.org/10.1007/978-0-387-49785-3_37.
15. Taniguchi C, Kawabata Y, Wada K, Yamada S, Onoue S (2014), Microenvironmental pH-modification to improve dissolution behavior and oral absorption for drugs with pH-dependent solubility. Expert Opin Drug Deliv 11, 4, 505–516.
16. Breda SA, Jimenez-Kairuz AF, Manzo RH, Olivera ME (2009), Solubility behavior and biopharmaceutical classification of novel high-solubility ciprofloxacin and norfloxacin pharmaceutical derivatives. Int J Pharm 371, 1, 106–113.
17. Myungjoo K, JaeYoul C, ByungHo S, DukKi K, JaehWi L (2009), Bioavailability enhancing activities of natural compounds from medicinal plants. J Med Plant Res 3, 1204–1211.
18. Fernández-Lázaro D, Mielgo-Ayuso J, Córdova Martínez A, Seco-Calvo J (2020), Iron and physical activity: bioavailability enhancers, properties of black pepper (bioperine®) and potential applications. Nutrients 12, 6, 1886.
19. Guo YG, Singh AP (2019), Emerging strategies for enhancing buccal and sublingual administration of nutraceuticals and pharamaceuticals. J Drug Deliv Sci Technol 52, 440–451.
20. Wani MC, Horwitz SB (2014), Nature as a remarkable chemist: A personal story of the discovery and development of Taxol. Anticancer Drugs 25, 5, 482–487.
21. Sohail MF, Rehman M, Sarwar HS, Naveed S, Salman O, Bukhari NI, Hussain I, Webster TJ, Shahnaz G (2018), Advancements in the oral delivery of Docetaxel: challenges, current state-of-the-art and future trends. Int J Nanomed 13, 3145–3161.
22. Fuoco D, Cohen J, Rosanelli L, McKibbon K (2020), Nanostructure lipid carrier delivery system, composition and methods. US Patent US 20230094753A1.
23. Fuoco D (2012), Classification framework and chemical biology of tetracycline-structure-based drugs. Antibiotics 1, 1, 1–13.

24. Liu ZX, Artmann C (2009), Relative bioavailability comparison of different coenzyme Q10 formulations with a novel delivery system. Altern Ther Health Med 15, 2, 42–46.
25. Shah AV, Desai HH, Thool P, Dalrymple D, Serajuddin ATM (2018), Development of self-microemulsifying drug delivery system for oral delivery of poorly water-soluble nutraceuticals. Drug Dev Ind Pharm 44, 6, 895–901.
26. Tran TH, Guo Y, Song D, Bruno RS, Lu X (2014), Quercetin-containing self-nanoemulsifying drug delivery system for improving oral bioavailability. J Pharm Sci 103, 3, 840–852.
27. Fuoco D, di Tomasso J, Boulos C, Morais JA (2015), Identifying nutritional, funtional, and qualityof life correlates with male hypogonadism in advanced cancer patients. eCancerMedicalScience 9, 569.
28. Fuoco D (2012), A new method for characterization of natural zeolites and organic nanostructure using atomic force microscopy. Nanomaterials 2, 1, 79–91.
29. Fuoco D (2015), Cytotoxicity induced by tetracyclines via protein photooxidation. Adv Toxicol 2015, 1, 787129.
30. Barani M, Sangiovanni E, Angarano M, Rajizadeh MA, Mehrabani M, Piazza S, Gangadharappa HV, Pardakhty A, Mehrbani M, Dell'Agli M, Nematollahi MH (2021), Phytosomes as innovative delivery systems for phytochemicals: a comprehensive review of literature. Int J Nanomedicine 16, 6983–7022.
31. Park JW, Lagniton PNP, Liu Y, Xu RH (2021), mRNA vaccines for COVID-19: what, why and how. Int J Biol Sci 17, 6, 1446–1460.
32. Alberts DS, Garcia DJ (1997), Safety aspects of pegylated liposomal doxorubicin in patients with cancer. Drugs 54, 4, 30–35.
33. Werner ME, Cummings ND, Sethi M, et al.et al. (2013), Preclinical evaluation of Genexol-PM, a nanoparticle formulation of paclitaxel, as a novel radiosensitizer for the treatment of non-small cell lung cancer. Int J Radiat Oncol Biol Phys 86, 3, 463–468.
34. Wang X, Ishida T, Kiwada H (2007), Anti-PEG IgM elicited by injection of liposomes is involved in the enhanced blood clearance of a subsequent dose of PEGylated liposomes. J Control Release 119, 2, 236–244.
35. Povsic TJ, Lawrence MG, Lincoff AM, Mehran R, Rusconi CP, Zelenkofske SL, Huang Z, Sailstad J, Armstrong PW, Steg PG, Bode C, Becker RC, Alexander JH, Adkinson NF, Levinson AI (2016), Pre-existing anti-PEG antibodies are associated with severe immediate allergic reactions to pegnivacogin, a PEGylated aptamer. J Allergy Clin Immunol 138, 6, 1712–1715.
36. Duarte I, Temtem M, Gil M, Gaspar F (2011), Overcoming poor bioavailability through amorphous solid dispersions. Ind Pharm 30, 4–6.
37. Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, Jessen L (1998), Enhanced bioavailability of itraconazole in hydroxypropyl-beta-cyclodextrin solution versus capsules in healthy volunteers. Antimicrob Agents Chemother 42, 7, 1862–1865.
38. Huang S, Huang Z, Fu Z, Shi Y, Dai Q, Tang S, Gu Y, Xu Y, Chen J, Wu X, Ren F (2020), A novel drug delivery carrier comprised of nimodipine drug solution and a nanoemulsion: preparation, characterization, in vitro, and in vivo studies. Int J Nanomedicine 15, 1161–1172.
39. Uchino T, Yasuno N, Yanagihara Y, Suzuki H (2007), Solid dispersion of spironolactone with porous silica prepared by the solvent method. Pharmazie 62, 8, 599–603.
40. Beg S, Swain S, Rizwan M, Irfanuddin M, Shobha Malini D (2011), Bioavailability enhancement strategies: basics, formulation approaches and regulatory considerations. Curr Drug Deliv 8, 6, 691–702.
41. Im K, Ravi A, Kumar D, Kuttan R, Maliakel B (2012), An enhanced bioavailable formulation of curcumin using fenugreek-derived soluble dietary fibre. J Funct Foods 4, 1, 348–357.
42. Shi L, Zhou J, Guo J, Gladden I, Kong L (2021), Starch inclusion complex for the encapsulation and controlled release of bioactive guest compounds. Carbohydr Polym 274, 118596.
43. Zhou Y, Li H, Yang YW (2015), Controlled drug delivery systems based on calixarenes. Chin Chem Lett 26, 7, 825–828.
44. Fuoco D, Cohen J (2020), Process for the purification of whey protein isolate and formulation thereof, Patent CA3086093A1.
45. Souto EB (Ed.) (2012), Patenting nanomedicines: legal aspects, intellectual property and grant opportunities, Springer Science & Business Media, New York City.
46. Al-Marzouqi AH, Elw HM, Shehadi I, Adem A (2009), Physicochemical properties of antifungal drug-cyclodextrin complexes prepared by supercritical carbon dioxide and by conventional techniques. J Pharm Biomed Anal 49, 2, 227–233.
47. Carrier RL, Miller LA, Ahmed I (2007), The utility of cyclodextrins for enhancing oral bioavailability. J Control Release 123, 2, 78–99.
48. Pouton CW (2000), Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and "self-microemulsifying" drug delivery systems. Eur J Pharm Sci 11, S93–S98.
49. Conniot J, Silva MJ, Fernandes J, Liana CS, Gaspar R, Brocchini S, Florino HF, Barata TS (2014), Cancer immunotherapy: nanodelivery approaches for immune cell targeting and tracking. Front Chem 105, 1–28.
50. Soni SK, Deseale SS, Bronich KT (2016), Nanogels: an overview of properties, biomedical applications and obstacles to clinical translation. J Control Release 240, 109–126.
51. Gao W, Zhang Y, Zhang Q, Zhang L (2016), Nanoparticle-hydrogel: a hybrid biomaterial system for localized drug delivery. Ann Biomed Eng 44, 2049–2061.
52. Polyak F, Boudovitch D (2023), Complexes comprising a carbohydrate and processes for their preparation, U.S. Patent Application No. 17/784,468.
53. Huang G, Huang H (2018), Application of hyaluronic acid as carriers in drug delivery. Drug Deliv 25, 1, 766–772.
54. Balakrishnan P, Lee BJ, Oh DH, Kim JO, Lee YI, Kim DD, Jee JP, Lee YB, Woo JS, Yong CS, Choi HG (2009), Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. Int J Pharm 374, 1, 66–72.
55. Cho HJ (2020), Recent progresses in the development of hyaluronic acid-based nanosystems for tumor-targeted drug delivery and cancer imaging. J Pharm Investig 50, 2, 115–129.
56. Zhong W, Pang L, Feng H, Dong H, Wang S, Cong H, Shen Y, Bing Y (2020), Recent advantage of hyaluronic acid for anti-cancer application: a review of "3S" transition approach. Carbohydr Polym 238, 116204.
57. Arshad R, Gulshad L, Haq IU, Farooq MA, Al-Farga A, Siddique R, Manzoor MF, Karrar E (2021), Nanotechnology: a novel tool to enhance the bioavailability of micronutrients. Food Sci Nutr 9, 6, 3354–3361.
58. Wang S, Su R, Nie S, Sun M, Zhang J, Wu D, Moustaid-Moussa N (2014), Application of nanotechnology in

improving bioavailability and bioactivity of diet-derived phytochemicals. J Nutr Biochem 25, 4, 363–376.
59. Polyakov NE, Kispert LD (2015), Water soluble biocompatible vesicles based on polysaccharides and oligosaccharides inclusion complexes for carotenoid delivery. Carbohydr Polym 128, 207–219.
60. Panyue W, Wendong K, Dirisala A, Toh K, Tanaka M, Li J (2023), Stealth and pseudo-stealth nanocarriers. Adv Drug Deliv Rev 198, 114895.
61. Salmaso S, Caliceti P (2013), Stealth properties to improve therapeutic efficacy of drug nanocarriers. J Drug Deliv 2013, 1, 374252.
62. Schöttler S, Becker G, Winzen S, Steinbach T, Mohr K, Landfester K, Mailänder V, Wurm FR (2016), Protein adsorption is required for stealth effect of poly(ethylene glycol)- and poly(phosphoester)-coated nanocarriers. Nat Nanotechnol 11, 4, 372–377.
63. Li M, Jiang S, Simon J, Pablick D, Frey M-L (2021), Brush conformation of polyethylene glycol determines the stealth effect of nanocarriers in the low protein adsorption regime. Nano Letters 21, 1591–1598.
64. Fuoco D, Poletti A, Forini N (2008), 3D Surface of natural zeolites investigate using high resolution microscopy. ICP – Rivista della Industria Chimica Italiana 35, 100–105.

**Cite this article as:** Boudovitch D, Sakaya A, Uzundurukan A, Leroux J-Y & Fuoco D, et al. 2023. Review of commercially available nano-drugs and nano-delivery systems: challenges and perspectives. 4open, **6**, 9.