An overview on oral drug delivery via nano-based formulations

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**ABSTRACT**

Oral drug administration is used for a large number of medications, intended to create a systemic effect in the body. Over the recent years, an increasing attention has been directed by pharmacists toward the development of successful formulations for oral drug delivery. However, this issue is still controversial in pharmaceutical technology with many limitations due to the numerous barriers against the absorption and permeability in the gastrointestinal tract. On the other hand, drug carriers play an important role in providing prolonged release and delivery and overcome the multiple barriers of maintaining appropriate bioavailability. Nano scaling of the particles, carriers, and polymers has also provided the capability to characterize and control materials in order to produce unique pharmaceutical components and structures. Furthermore, personalized healthcare, rational drug design, and site-specific targeted drug delivery are some of the profits gained from a nano-based formulation approach. This review aimed to evaluate the evidence on some different types of nanoscaled drug delivery systems, which allow for the delivery of small-molecule drugs and facilitate the merging of larger particles, such as nucleic acids, peptides, and proteins. The delivery of these molecules to the exact target areas inside the body can be accomplished, which would decrease systemic adverse effects and allow for more effective application of the pharmaceutical preparations.

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**Introduction**

Oral route has been known as the most appropriate, easily applicable, inexpensive, convenient, and preferred way for drug administration. However, the majority of available pharmaceutical preparations have shown poor absorption and permeability through gastrointestinal barriers. This failure, due to the structural properties, such as molecular size and hydrophilicity, would be followed by a decrease in bioavailability, resulting in the non-fulfillment of the expected pharmaceutical effect. Furthermore, the bioavailability of therapeutic nanoparticles, peptides, and proteins via the oral administration route is almost nil as a result of proteolytic degradation, mucosal barriers, and intestinal efflux pumps. Meanwhile, the enhancement of the absorption and bioavailability of the so-called pharmaceuticals is quiet a fundamental challenge (1-3). Buoyant nanotechnology, as a novel promising approach, offers several innovations to elucidate the supposed complication (4, 5). This nanotechnology has been also used for pharmaceutical purposes, which is resulted in the enhancement of the bioavailability of the oral medications (6, 7). This may happen through a size reduction from 1 to 100 nanometer scale, which considerably results in higher surface area, dissolution, and absorption of the particles (8, 9). Nano-based formulations cover liposomes, lipohydrogel nanocarriers, and inorganic/metallc nanoparticles. Novel approaches and applications, such as nanosuspension coating technique, have been generated in this regard (10, 11). On the other hand, the assessment of the stability of the aforementioned nanoparticles is of similar importance in this domain (12, 13). Moreover, the unique properties and side effects of nanomaterials on the human body have become a subject of extreme interest. These unique effects are due to the high surface area and the consequent reactive surface chemistries of the named particles. Biocompatibility and capability of the nanoparticles, which may depend on their size, shape, and charge, should be assessed in order to prepare novel formulations and polymers (14, 15). Nanoparticles, having a rapid intestinal uptake, can accumulate, and consequently become toxic for the cells of different organs (e.g., liver, kidney, or lungs) if administered for prolonged periods. This is an unavoidable characteristic of these particles that should be concerned for in vivo applications (16, 17). The aim of this study was to investigate the evidence on the current nanoparticle-based formulations and their applications in the oral route of drug delivery. The focus of the study was on different nanoparticulate formulations, stability, bioavailability, biocompatibility, toxicity, and morphology to facilitate the efficient application of these medications.

**Oral Drug Delivery**

Drug administration via oral route allows for the achievement of both local and systemic effects; therefore,
it is highly preferred by the patients. Moreover, this route of drug administration entails the advantages of being easy and painless. In addition, this route of delivery can be utilized for the administration of different time-release forms, including slow-, sustained-, or delayed-release, of medical preparations, thereby fulfilling the need of a wide scope of the drug delivery market (1, 13).

In conventional oral drug delivery systems, including solid (e.g., tablets and capsules) and liquid (e.g., solutions and suspensions) dosage forms, there is very little control over the release of drug (18). Conventional oral formulations have some drawbacks. In this regard, the delivery of effective concentrations of these formulations to the target site can be achieved by the recurrent administration of high doses, which in most of the cases results in overdosing or continuously changing irregular, random, and often sub-therapeutic plasma concentrations, thereby inducing considerable side effects (19, 20). This issue has underscored the urgent need for performing studies targeted toward the enhancement of oral absorption in the recent years where nanostructured preparations may be a key component.

**Oral route limitations in drug delivery**

In the gastrointestinal tract (GI), the absorption, permeability, and finally bioavailability of the drug molecules would be reduced due to many barriers existing in this route (3, 21, 22). The barriers include wide pH range of the GI tract, enzymatic environment, degradation of especially proteinaceous drug molecules, and reduced absorption of these molecules. These challenges are produced due to either the enterocytes or the tight junctions of the intestinal cells. Generally, the GI tract is composed of a number of sections functioning together with mechanical and biochemical progressions to support converting foodstuff into energy. These molecules would have different ways to enter the bloodstream in which they face various barriers (23, 24). Figure 1 illustrates the schematic presentation of the obstructions existing in the GI tract, the different transcellular, paracellular, and active diffusion through receptor-mediated endocytosis, and carrier-mediated transport.

![Figure 1](Image 50x121 to 300x249)

**Table 1** summarizes information regarding GI tract barriers to proteinaceous absorption.

| Stomach | Intestine | References |
|---------|-----------|------------|
| Enzymes | Absorption |            |
| Pepsin | Enterocytes or tight junctions of the intestinal cells (25, 26) |

**Nano-based formulations**

Nanomedicine could be well-defined as the knowledge of controlling, employing studying, and manufacturing structures or carriers/devices in the “nanometer” scale and “nanoparticles”. Nanoparticles stand for “particles in one billion” in its wide-ranging explanation and is defined as particles with size ranges of 10-1000 nanometers. Nanoparticles have been recognized as a unique and promising approach due to retaining very high surface area to volume ratios. In addition, this approach has addressed the limitations of the currently available methods in order to enhance the dissolution rates of poorly water-soluble drugs. It was also shown to be more stable than other colloidal preparations in the GI tract. Moreover, they are capable of being manipulated easily owing to their physical and chemical characteristics, drug-release profile, and biological behavior. These particles are able to absorb and/or encapsulate a drug, thereby protecting it contrary to chemical and enzymatic degradation (15, 27, 28). Many different formulations have been introduced by nanomedicine, such as inorganic/metallic nanoparticles, polymeric nanoparticles, liposomes, and lipohydrogel nanocarriers, which approve absorption through the intestinal epithelium (29, 30). The schematic presentation of drug incorporation within these nanoparticles is depicted in Figure 2. Nanoparticles possess a wide variety of applications in medical field. Table 2 presents some orally administered nanomaterials reported in different studies.

**Inorganic/metallic nanoparticles**

Inorganic nanoparticles covering silver, iron oxide, and gold nanoparticles, as well as the quantum dots, which possess
intrinsic magnetic, optical, and electrical properties, pave the way for the emergence of innovative technology. Accordingly, several recent efforts have been targeted toward the application of these nanoparticles in the biomedical field (40, 41). Metallic nanoparticles have a good capability of creating multifunctional nanoprobes for in vivo applications, both in imaging and therapeutic procedures, due to having excellent intrinsic physical assets and versatile surface. The use of these nanoparticles sequentially increase the need for the particles due to their biocompatibility, colloidal stability, and high efficacy (42). The inorganic nanoparticle-mediated probes have been exploited for biomedical purposes for many years. However, the investigation of the in vivo behavior of these nanoparticles, mainly the pharmacokinetics and unintendedly made protein corona, are still at a preliminary stage. They also attracted attention regarding their applicability in the enhancement of therapeutic efficacy (43).

**Table 2**: Examples of the nanomaterials used via oral route of administration

| Oral Nano-based Formulations | Type                        | Applications                       | References |
|------------------------------|-----------------------------|------------------------------------|------------|
| Insulin loaded nanoparticles | Polymeric nanoparticle      | Diabetes management                | (31, 32)   |
| Paclitaxel loaded SLNs with hydroxypropyl-b-cyclodextrin (HPCD) | Polymeric nanoparticle      | Cancertherapy                       | (33, 34)   |
| Nanosilver                   | Inorganic/metallic nanoparticle | Mouthwash, toothpaste, dental composites | (35, 36)   |
| Nanogold                     | Inorganic/metallic nanoparticle | Oral cancer diagnosis              | (37-39)    |
Biocompatibility of nanoparticles has been achieved by either in situ coating throughout the synthesis or after surface modification via several ligands. A multi-targeting nanoparticle system, consisting of two or more targeting phases or stimuli-responsive targeting moieties, shows an encouraging targeting strategy. It can be also supposed that the eventual goal of developing nanomedicine is their clinical application. Therefore, it is essential to have sufficient supply of high-quality nanoparticles (39). Although a low number of these particles have been approved for clinical use, most of them still require overcoming potential toxicity problems. It would be predictable that some of the inorganic nanoparticles, such as gold colloids, will overcome these barriers and ultimately enter the clinical studies (44, 45).

**Polymeric nanoparticles**

Biodegradable polymeric nanoparticles have gained a great concern and considerable attention by means of being a potential drug delivery agent considering their applications in the controlled release of drugs and targeting particular biological ligands or targets. They have been also used in order to carry DNA in gene therapy processes and deliver proteins and peptides through the oral route (46).

Polymeric micelles are characterized by a core-shell structure. The viscosity of the micellar core may influence the physical stability of the micelles and drug release. The biodistribution of the micelle is mainly dictated by the nature of the shell, which is also responsible for micelle stabilization and interactions with plasma proteins and cell membranes. The micelles can contain functional groups at their surface for conjugation with a targeting moiety (47). Polymeric micelles are mostly small (10-100 nm). Pharmaceutical preparations should maintain their integrity for an adequate quantity of period after injection through the body for effectual delivery to their effective sites of action. Attachment of antibodies or sugars, or introduction of a polymer sensitive to variant temperatures or different pH points could also be valuable (48).

**Liposomes**

Liposomes are a form of vesicles that consist either of many, few, or just one phospholipid bilayers. The polar character of the liposomal core enables the polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. They consist of small vesicles composed of unilamellar or multilamellar phospholipid bilayers surrounding one or several aqueous compartments (49).

In addition, the charge, as well as lipid composition and size (ranging from 20 to 10,000 nm) of liposomes can vary. Many liposome formulations are rapidly taken up by macrophages. Cationic liposomes and lipoplexes have been extensively investigated for their application in non-viral vector-mediated gene therapy (15, 19, 49). The use of molecules, such as polyethylene glycol, to prevent liposome recognition by phagocytic cells led to the development of the so-called ‘stealth’ liposomes with longer circulation times and increased distribution to peripheral tissues in the body (50). Moreover, targeting device or homing ligand can be included at the external surface of the liposome in order to obtain target cell specificity (50, 51). Another approach is the design of target-sensitive liposomes or fusogenic liposomes that become destabilized after binding and/or internalization into the target cells (49, 52). Liposomes possess the advantages of intact delivery to tissues and cells (enabling site-specific and targeted drug delivery), ability to be used for both lipophilic and hydrophilic drugs, and decreased toxicity to other tissues and cells. Furthermore, the size, charge, and other characteristics of the liposomes can be altered (49, 50, 52, 53). On the other hand, some disadvantages of using these spherical vesicle in drug delivery systems include the tendency to be taken up by the cells of RES and slow release of drug when absorbed by phagocytes (50, 54).

**Lipohydrogel nanocarriers**

Hydrogels are three-dimensional, hydrophilic, and polymeric networks that are capable of absorbing large amounts of water or biological fluids. These systems are composed of homopolymers or copolymers and are insoluble due to the existence of chemical crosslinks (tie-points, junctions) or physical crosslinks, such as entanglements or crystallites. Hydrogels display a thermodynamic compatibility with water, which permits them to swell in aqueous media. They are utilized in the regulation of drug release in reservoir-based, controlled release systems or as carriers in swellable and swelling-controlled release strategies. Hydrogels as environment and stimuli-sensitive gel systems modulate release in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences.

In these systems, release can be designed to occur within the specific areas of the body (e.g., within a certain pH of the digestive tract) or also via specific sites (adhesive or cell-receptor specific gels via tethered chains from the hydrogel surface) (15, 53).

**Bioavailability**

Water solubility, dissolution, and GI permeability are the most important factors that control the speed and amount of the finally absorbed drug, and consequently its bioavailability (55). The main objective of nanoparticulate forming of the medical preparations is to overcome the intestinal barriers and enhance the bioavailability (56). Integration of the drug molecules in different nanostructured carriers offers immense advantages by facilitating a better biodistribution of active compounds, protection against degradation,
targeting, expulsion, and more efficacious communication with biological barriers. Due to the small size of the nanoparticles, they can pass through the blood-brain barrier and function at cellular dimensions (57, 59).

**Stability of nanoparticles**

Evaluation of the stability of the nanoparticles is of paramount importance in oral drug delivery approach and its pharmaceutical effects. This is accomplished through the assessment of the size, shape, surface, drug loading capacity, and physical appearance of these particles. (59, 60). Nanoparticles possess a faster and better drug-release profile and can cross the blood-brain barrier due to their particle size, compared to microparticles (61-63). Stability of nanoparticles is in close relation to their surface properties where the hydrophilicity/hydrophobicity balance, and the surface charge of the particles would change their final adsorbed extent by the immune proteins (2, 60).

**Biocompatibility and toxicity concerns**

Use of nanoparticles for biomedical purposes has been reported to have an exponential growth in the past few years. Although our knowledge of the safety of these nanoparticles has not yet reached a reliable grade, new drug delivery systems are brought to clinical application. Adverse side effects or desired outcomes related to these compounds could be investigated by preliminary and complementary animal studies (64). There are many factors affecting the toxicity of nanoparticles, including high surface area, particle size, coarseness, shape, surface charge, and surface coating molecules (65). The nanoparticles ought to be well designed to result in the lowest cell toxicity. The aforementioned parameters would also determine the biocompatibility of the nanoparticles and after reaching the systemic blood circulation, binding to plasma components (albumin) and degradation products for complex and novel copolymers will be of utmost importance (66, 67). The different mechanisms of the toxicity of the nanoparticles include misfolding and protein fibrillation in the diseases of the central nervous system and chronic inflammation in the problems related to the respiratory system made by frustrated phagocytosis or reactive oxygen species (ROS) production (68).

**Future prospect of nano-based formulation**

As outlined in the various sections above, several types of nanoparticles can be used for the delivery of the pharmaceutical agents via oral drug administration route. Regarding this, the application of nanomedicine and nano-based formulations and systems is certainly the trend that will continue to be adopted as an important research area and development for the coming decades. However, it would be necessary to study and manipulate the long-lasting cytotoxicity of nanoparticles (69). Since nanoparticles are supposed to go through absorption by means of M-cells or enterocytes, it would be logical to consider the manner by which they will possibly interact at these sites. However, the progress of consistent tests with following technologies for nano-based formulations is still obligatory (70).

**Conclusion**

Polymeric nanoparticles possess various beneficial characteristics for the oral administration of peptides and proteins. These nanoparticles facilitate the achievement of the appropriate properties of prolonged release and protection from proteinaceous enzymatic environment. Nonetheless, many studies are still required to define the exact mechanism of the uptake and consequent elimination of nano-based formulations. As a final point, nano-based drug delivery offers a limitless and beneficial potential for oral preparations allowing better biomedical outcomes.

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**Conflict of interests**

The authors declare no conflict of interest or competing financial interest in the present study.

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