Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN

0976-9595

Review Article

Calcium Phosphate Based Micro and Nanoparticles in Oral Drug Delivery: Formulation Approaches, Intestinal Fate, and Bioavailability Enhancement: A Review

Mital A. Patel, Tejal G. Soni*

Faculty of Pharmacy, Dharmsinh Desai University, Nadiad, Gujarat, India

*Corresponding author: tejalsoni.ph@ddu.ac.in

Received: 25-02-2026; Accepted: 09-03-2026; Published: 30-03-2026

https://doi.org/10.55218/JASR.2026170305

ABSTRACT

The emergence of calcium phosphate (CaP) based micro and nanoparticles has been of much interest as a novel approach to solving the inherent problems associated with the oral delivery of drugs, namely low solubility, instability, and bioavailability of most therapeutic agents. The paper is a review that gives a complete discussion on the use of CaP as a biocompatible, biodegradable and pH-responsive carrier during oral delivery. The physicochemical versatility of CaP provides the opportunity to make drug delivery systems able to deliver controlled release, targeted absorption in the intestine, and a greater bioavailability. The different synthesis strategies, including wet precipitation, sol-gel processes, spray drying, and biomimetic mineralization, allow a solid control of morphology and drug encapsulation capacity of particles. Moreover, the intestinal fate of CaP systems indicates their capacity to protect drugs in acidic gastric conditions and release and uptake site-specifically in the intestine. Their practical potential is noted in case studies, such as the solubility of compounds with low solubility (such as curcumin, paclitaxel, and raloxifene deliveries). Although there are current shortcomings like aggregation and scale-up biases, new hybrid and surface-modified CaP systems are resolving them. Altogether, CaP-based carriers can be discussed as an effective, safe, and scalable platform for delivering oral medication in the next generation, at the same time, effective for pharmaceuticals and biologically compatible.

Keywords: Calcium phosphate nanoparticles, Oral drug delivery, Bioavailability, Controlled release, pH-responsive systems.

INTRODUCTION

The most preferred method of administration is oral drug delivery as it is convenient, patients can take it and its production cost is low. Nonetheless, a considerable percentage of active pharmaceutical ingredients (APIs) are characterized by low aqueous solubility, low permeability and instability in the gastrointestinal (GI) tract, which in combination causes low bioavailability [1]. These issues are particularly strong with Biopharmaceutics Classification System (BCS) Class II and IV drugs, in which dissolution and intestinal absorption are rate-limiting stages. Consequently, the improvement of the solubility, dissolution, and stability of the drug to be delivered orally continues to be a significant objective of drug formulation research in pharmaceutical studies [2]. To overcome these obstacles, new methods of drug delivery have arisen by introducing the use of particulate drug delivery systems to enhance drug solubility, stability, and absorption. Micro and nanoparticle carriers have the ability to alter the rate of drug release, to shield labile drugs against degradation in the stomach, and to target the release of drugs at particular locations in the intestine. Inorganic particulate systems have been explored among them because they are physicochemically stable, their surface chemistry can be tuned, and they can be combined with different drugs [3]. Silica, titanium dioxide and calcium phosphate (CaP) have been studied towards such applications, with CaP of particular interest due to its natural occurrence in the human body and good biological characteristics.

Calcium phosphate is a biocompatible, inorganic compound that is present in the bone and teeth, and has a long history of application as a pharmaceutical excipient and biomaterial in orthopedic and dental problems. During the last years, it has become a promising additive to oral drug delivery systems because of its peculiarities, which are its pH-dependent solubility, the ability to be exchanged and buffer capacity [4]. CaP is dissolved in acidic gastric fluid to release calcium and phosphate ions and this is precipitated again under intestinal pH conditions, contributing to the delivery of controlled drug release and absorption improvement. CaP particles are particularly beneficial to oral delivery at the micro- and nanoscale. In some cases, nanoparticles, especially, provide superior surface area, enhanced mucoadhesion, as well as the capacity to interact closely with epithelial surfaces, hence enhancing retention and uptake of drugs in the small intestine [5]. Furthermore, CaP biodegradability removes any fears of accumulation over time and CaP GRAS (Generally Recognized As Safe) status leads to regulatory acceptability of the pharmaceutical use.

Some of the researches have been able to show the ability of CaP-based carriers in increasing the solubility and oral bioavailability of drugs with low solubility, including curcumin, raloxifene and

paclitaxel. These systems operate via several mechanisms, which are accelerated dissolution rate, supersaturation and formation of a favorable micro-environment in the intestinal surface [6]. Therefore, CaP-based micro- and nanoparticles systems are a strong, safe, and efficient system to design next-generation oral preparations. The aim of the review is to critically summarize the formulation strategies, the intestine fate, and the mechanism of the enhancement of bioavailability of CaP-based micro- and nanoparticles in oral drug delivery, and their potential to be applied in the clinical environment.

Calcium Phosphate as A Pharmaceutical Excipient and Carrier

CaP has been widely applied in the pharmaceutical, food and biomedical sectors because of its biocompatibility, biodegradability and its safety. Being a natural inorganic mineral, it is the primary component of bones and teeth, so it can be easily adopted into the context of bio-use. It is chemically similar to the human hard tissues, physiologically tolerable, which makes it a good choice in delivering drugs by oral and systemic routes [7]. A number of varieties of calcium phosphate have been researched and exploited, each with a varying degree of crystallinity, solubility and calcium-phosphorus (Ca/P) ratio. Hydroxyapatite (HAp) [Ca 10(PO 4)6(OH) 2], tricalcium phosphate (TCP) [Ca 3(PO 4) 2], and amorphous calcium phosphate (ACP), a non-crystalline intermediary phase, are the most widespread. The differences in these materials, specifically their physicochemical properties, have a direct impact on drug loading, release and dissolution. As an example, ACP is more soluble and reacts to different surfaces, which is the reason it can be used in cases of fast-drug release, and HAp is better suited to sustained-release formulas due to its crystalline stability [8]. Pharmacologically, calcium phosphate is a pharmacopeial inert excipient and Generally Recognized As Safe (GRAS) by the regulatory agencies. It finds application as a diluent, filler and tablet disintegrant in oral solid dosage forms because of its flowability, compressibility and its chemical inertness. Moreover, it features a buffering capacity that can stabilize the acid-labile drugs within the gastrointestinal tract of the body at a near-neutral micro-environment [9]. Another significant strength is the biocompatibility and safety profile of calcium phosphate. After this, it is absorbed in calcium and phosphate ions, which are vital physiological nutrients. CaP does not cause inflammatory or toxic effects and can be readily eliminated by the body, as opposed to synthetic polymers or metallic nanoparticles. The products of its degradation are involved in the natural bone mineral metabolism, and therefore, its systemic load is low [10].

CaP as a carrier drug has versatile loading properties by adsorption or co-precipitation. Depending on the surface charge, porosity, and ion exchange capacity, it is possible to incorporate a wide variety of different drug molecules, including small hydrophobic molecules to large molecules such as peptides and nucleic acids. Phosphate and carboxyl groups of drugs are also highly affinity with Ca^{2+} and the stable but reversible interactions are also promoted. Notably, pH-sensitive solubility of CaP, being insoluble in intestinal pH but dissolvable in gastric acid, allows site-specific and targeted drug delivery, sparing sensitive drugs in the gastric environment [11]. These positive qualities have seen calcium phosphate transform from an ordinary excipient to a practical delivery vehicle with the capability of enhancing oral absorption and bioavailability of drugs. Its multifunctionality combines the delivery vehicle between excipient and active, and therefore, it is a fundamental element in designing the next-generation oral drug delivery systems.

Micro and Nanoscale Calcium Phosphate Particles

The particle size is a critical variable that determines the physicochemical behaviors, biological interactions/response as well as drug delivery activities of CaP-based carriers. CaP particles can be produced in the micrometer (1–100 μM). These two size scales give significantly different surface, dissolution and absorption properties that are directly related to the increase in oral bioavailability [12]. Microscale CaP particles have been utilized traditionally as excipients or bulk carriers in oral formulations. They offer high drug loading capacity, excellent flowability, and consistent mechanical properties to be used in the formulation of tablets or capsules. They, however, have low surface area and slower rates of dissolution, which makes them interact with the intestinal mucosa less and have slower kinetics of drug release. Such characteristics render them useful in sustained-release or matrix types of oral formulations as opposed to rapid-release systems [13].

Conversely, the use of nanoscale CaP particles has transformed the use of oral drugs due to their size-specific benefits. They have a high surface-to-volume ratio, which allows better drug adsorption and also improved interaction with the mucosal membrane, which improves drug permeation and bioavailability. Furthermore, nanoparticles can traumatize mucus layers and be incorporated by intestinal epithelial cells by endocytosis or paracellular transport, which are normally not open to larger microparticles. This is the increased absorption behavior that has been shown to increase the absorption of poorly soluble drugs and biomacromolecules [14]. Moreover, the nanoscale confinement effect changes the dissolution dynamics of CaP to release the encapsulated drugs faster and higher ion exchange with the surrounding medium. The hydrolysis of CaP nanoparticles at the bowel pH provides a localized supersaturation, which sustains an ideal concentration gradient that facilitates the sustained absorption. Nevertheless, aggregation of nanoparticles is still a problem; it is commonplace to stabilize nanoparticles with surfactants or polymer coating.

It is demonstrated that CaP nanoparticles are superior to microparticles in cellular uptake, dissolution and intoxication, especially in hydrophobic and pH-sensitive drugs. However, microscale carriers are still useful in cases where a specific delivery or control is needed. Micro- and nanoscale systems, therefore, have their own unique but complementary roles in the wider context of oral drug delivery application with nanoscale formulations being of more appeal to clinical translation because of their improved absorption and pharmacokinetic capabilities [15].

Methods of Preparation of Calcium Phosphate Micro and Nanoparticles

The production process of CaP particles is one of the key factors that determine their physicochemical properties, including size, morphology, crystallinity, and surface area, which also affect the efficiency of drug loading and release. The strategies that have been

developed to make CaP particles on the micro- and nanoscale include: wet chemical precipitation, sol-gel synthesis, spray drying and biomimetic processes [16]. All methods have certain merits in terms of the required particle properties and the needed pharmaceutical use (Fig. 1).

Wet chemical precipitation

The most commonly used technique of CaP particle synthesis is wet chemical precipitation due to its simplicity, scalability, and the capability of producing particles with adjustable composition. It entails controlled mixing of aqueous calcium and phosphate salt solutions under given conditions of pH and temperature and results in the nucleation and growth of CaP crystals. The parameters of the product, i.e. Ca/P ratio, reaction time, and stirring speed, define it as hydroxyapatite (HAp), tricalcium phosphate (TCP), or amorphous calcium phosphate (ACP). This technique is capable of producing micro and nanoscale particles; particle size reduction is usually done by the addition of surfactants or ultrasonication [17].

Sol–gel method

The sol-gel process presents exact control over particle morphology and homogeneity. It entails the hydrolysis and condensation of calcium and phosphate in alcoholic or aqueous media to form a colloidal sol that transforms to a gel network. CaP particles are dried and then subjected to calcination, producing pure and uniform particles with high purity. The sol-gel route enables drug molecules to be incorporated in the porous matrix during the synthesis process and this gives it controlled-release properties. Nonetheless, the procedure may be lengthy and drying conditions may be sensitive to the process and affect crystallinity and porosity [18].

Spray drying

The use of spray drying is a scaled and fast procedure that allows the generation of spherical CaP micro- or nanoparticles. In this process, a suspension or a solution of CaP precursors (and perhaps drug molecules) is dispersed into a hot air jet, resulting in the immediate evaporation of a solvent and the formation of particles. The method enables co-precipitation of drugs with a carrier matrix, which gives even distribution through the CaP structure. Importantly, spray drying can be used especially to make composite CaP systems more mechanically stable and dispersible by adding polymers or lipids. It is very appropriate to be used in production at the industrial scale because of its reproducibility and being able to operate continuously [19].

Biomimetic synthesis

Biomimetic techniques mimic physiological mineralization processes at mild conditions, aqueous conditions, and simulate body fluid (SBF) to direct CaP nucleation. These mild reaction conditions allow the encapsulation of temperature-sensitive or biologically active molecules, including peptides and enzymes, without destruction. The resulting particles have high biocompatibility and porosity control. The biomimetic synthesis is similar *in-vivo* mineralization as CaP particles synthesized have comparable surface properties with biological apatite, which can be used to improve intestinal adhesion and bioavailability [16].

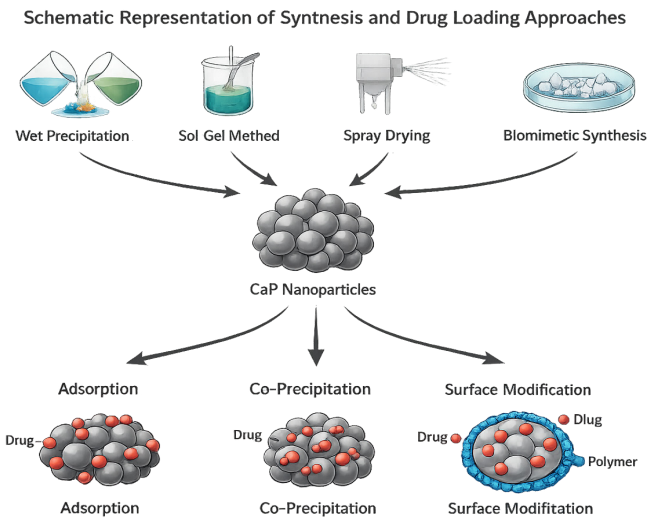

Fig. 1: Schematic representation of synthesis and drug loading approaches of CaP nanoparticles

Drug Loading and Release Mechanism

The rate of effectiveness of a drug delivery system is very dependent on the incorporation of a drug in the carrier and the eventual release of the drug under physiological conditions. Drugs may be incorporated into the matrix of calcium phosphate (CaP)-based carriers during synthesis by adsorption, co-precipitation, or encapsulation. The mechanisms have a direct impact on loading capacity, stability and release kinetics of the drug [20]. The simplest process is adsorption, which is usually the physical adherence of drug molecules to the CaP surface by means of electrostatic, hydrogen bonding, or van der Waals interactions. CaP surface charge and adsorption efficiency are highly dependent on their surface area, given the specific surface area and crystallinity. An example is amorphous calcium phosphate (ACP) and nano-hydroxyapatite (nHAp), which have a higher surface energy and porosity, which ensures that they are better adsorbers than crystalline tricalcium phosphate (TCP). Adsorption is also the best procedure in heat and solvent-labile drugs, and is able to maintain the biological activity of such drugs during formulation [21].

On the other hand, co-precipitation provides the opportunity to become entangled in the crystal lattice of CaP during the formation of particles. In this case, the reaction medium contains the drug, whereas calcium and phosphate ions precipitate, carrying the drug molecules with them in the developing matrix. Through this approach, a greater drug encapsulation efficiency and extended-release profiles are frequently achieved because the encapsulated drug is slowly diffused outside of the structure of the CaP. Nevertheless, co-precipitation has to be greatly optimized to avoid drug degradation in the synthesis, particularly in the case of delicate biomolecules like peptides or proteins. pH-sensitive release is one of the most useful aspects of CaP-based systems. CaP is a pH-responsive carrier that can be utilized in oral delivery because it is scarcely soluble in neutral or basic pH and is soluble in acidic conditions. Once it is ingested, CaP can survive the acidic gastric environment, which prevents the drug from degrading. At the intestinal pH (approximately 6.8–7.4),

slow dissolution of CaP takes place, liberating a drug and ions in a regulated process. The feature guarantees site-specification release, which increases absorption of the drug at intestinal locations where absorption is maximum [22].

Along with pH sensitivity, the release is also regulated by ion exchange and diffusion processes. With the CaP-intestinal fluids interaction, the calcium ion is exchanged with the hydrogen or sodium ion, which facilitates partial dissolution and diffusion of encasement drugs through the porous structure. The release rate can be manipulated through the adjustment of synthesis factors (crystallinity, porosity, particle size, and surface modification using polymers or surfactants). It is particularly useful in drugs having low solubility because sustained and controlled release behavior by CaP carriers is particularly beneficial, as it maintains a longer concentration gradient on the intestinal membrane. It has been demonstrated that CaP nanoparticles containing hydrophobic drugs (e.g., curcumin, paclitaxel, raloxifene) have high dissolution rates and longer release durations than free drugs and thus result in improved oral bioavailability [23]. Thus, multi-mechanistic release control plus physiological responsiveness contributes to CaP-based systems: CaP-based systems offer versatile delivery of therapeutic agents, allowing for the balance of protection, stability, and sustained release of therapeutic agents.

Intestinal Fate of Calcium Phosphate–Based Particles

The CaP-based micro- and nanoparticles, after being taken orally, experience a series of physicochemical changes as they pass through the GI tract. Their exposure to gastric and intestinal environments, release of ions and biological absorption processes are all the factors that predetermine the success of oral drug delivery. Intestinal fate of these carriers is determined by their composition, size, surface properties and crystallinity [24, 25]. CaP is partly dissolved in the stomach in a highly acidic environment (pH 1.2-2.0) to produce calcium and phosphate ions. The process is advantageous in the case of acid-labile drugs, since the CaP matrix has a buffering effect, which prevents the degradation of the encapsulated drug. Additionally, the dissolution does not occur fully, especially in the case of hydroxyapatite (HAp) and tricalcium phosphate (TCP), and such particles are able to enter the intestine with a significant portion of their structure intact. Calcium ion release may have temporary effects on gastric physiology by changing the local ionic strength and microenvironmental pH, which can mediate the effect of mucosal permeability [25]. When passing to the small intestine (pH 6.5-7.4), CaP particles are faced with a mildly basic environment, as well as an environment of bile salts and digestive enzymes. In this case, there is a possibility of partial reprecipitation of calcium and phosphate ions to create temporary nanoclusters or amorphous phases on the intestinal mucosa. These frameworks increase mucus adhesion and could serve as drug depots which promote sustained release of local drug and long resident time. In addition, the nanosized CaP particles are capable of either being endocytosed by M-cells in the Peyer's patches or trapped by paracellular transport through tight junctions, resulting in an improved systemic drug absorption [26].

The ion-exchange properties of the CaP are very critical in intestinal bioavailability. The calcium ions also react with the phosphate and carbonate ions in the intestinal fluids and the phosphate part can form complexes with the cationic drugs, which keep them stable in the solution. This irregular balance between the dissolution and reprecipitation enables CaP to be an extension of a controlled-release depot as well as a bioavailable ion source, establishing the optimum pharmacokinetic absorption of drugs.

Also, CaP particle stability may depend on the presence of bile salts. Although bile components can potentially facilitate partial dissolution, they can also facilitate the dispersion of nanoparticles, as they reduce aggregation. This stability-to-solubility ratio guarantees that CaP nanoparticles can be bioavailable to interact with intestinal epithelial cells to enhance overall pharmacokinetic profiles. The sum of the above-mentioned has shown that the CaP particles have a dual action; they are used to protect the drug in the stomach and release it with controlled release and improved absorption in the intestine. The most important factor to consider in the design of effective CaP-based oral formulations is to understand these changes so as to ensure that the bioavailability is reached and stays stable throughout the GI tract (Fig. 2).

Role of Calcium Phosphate Particles in Enhancing Oral Bioavailability

The physical ability to increase the oral bioavailability of poor solubility drugs is one of the key problems in pharmaceutical development. Carriers of CaP have become effective bioavailability enhancers because they possess multiple physicochemical and biological characteristics. The processes by which CaP particles enhance the absorption of oral drugs are accelerated dissolution, formation of a good microenvironment, controlled release mediated by ions, and increased mucosal attachment [27]. Solvency enhancement is one of the most important mechanisms. Hydrophobic molecules of drugs that are wet by CaP nanoparticles can be easily dispersed due to their large specific surface area and surface energy. This enhances surface contact, which favors dissolution, resulting in greater apparent solubility and faster absorption beginning. Moreover, the messaging of KaP at intestinal pH conditions may produce localized supersaturation, which will sustain a high concentration gradient

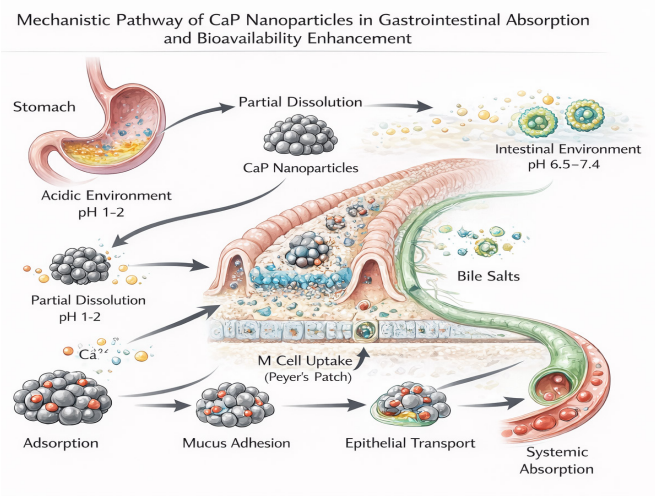

Fig. 2: Mechanistic pathway of CaP nanoparticles in GI absorption and bioavailability enhancement

next to the mucosal surface and will facilitate passive diffusion of the drug within intestinal membranes [20, 28].

The other relevant process is the alteration of the microenvironment. When CaP is dissolved in the intestinal fluid, calcium and phosphate ions are released, which temporarily changes the local pH and ionic environment. This buffer is capable of averting the recrystallization of oversaturated drug solutions, hence maintaining a favorable atmosphere of perpetual absorption. In addition, the ion release can temporarily influence tight junctions between epithelial cells, increasing paracellular permeability without having cytotoxic effects.

Mucosal adhesion and retention are also very important in bioavailability enhancement. CaP nanoparticles have surface chemistry and charge that facilitate their adhesion to intestinal mucus and epithelial surfaces, extending the retention period of the absorption site. This prolonged contact gives an increased opportunity of drug permeation and uptake via endocytic or transcellular pathways. Moreover, the contact between calcium ions and intestine proteins may allow temporary control of the membrane fluidity, enhancing the transcellular transfer of the drug [29]. These mechanisms have a cumulative effect that results in more substantial systemic drug exposure than the traditional formulations. Research has also indicated an increase in oral bioavailability of poorly soluble drug delivery systems like curcumin, paclitaxel, and raloxifene up to two to four times with CaP nanoparticles. Therefore, CaP systems are not only passive carriers, but they are active modulators of the intestinal microenvironment; hence, they can be used as a highly effective next-generation oral delivery strategy.

Applications of Calcium Phosphate-Based Systems in Oral Drug Delivery

Carriers based on CaP have been effectively utilized to deliver orally a wide range of therapeutic molecules, including poorly soluble small molecules, peptides, hormones, antioxidant and anticancer agents. Physicochemical adaptability enables the encapsulation of hydrophobic and hydrophilic drugs, and this makes them useful in a variety of pharmaceutical applications [30].

The CaP nanoparticles have shown exceptional prospects in increasing the solubility and bioavailability of hydrophobic drugs like curcumin, paclitaxel, and resveratrol among small-molecule drugs. They have low oral absorption, which is usually characterized by a low aqueous solubility and first-pass metabolism. The addition of them to the CaP matrices enhances dissolution and stability and is accompanied by pH-dependent ion exchange to release the material slowly in the intestine. An example is CaP-curcumin nanocomposites, which exhibited a 3.5 times larger oral bioavailability than free curcumin mainly because of the increase in mucosal adhesion and controlled dissolution [31].

The oral delivery of biomacromolecules like insulin, bovine serum albumin (BSA), and enzymes, which are usually unstable in the GI tract, has also been done using CaP carriers. These labile molecules can be enclosed in biomimetic CaP without being denatured due to the mild synthesis conditions. Moreover, the CaP buffer property prevents the destruction of proteins as a result of acidic gastric activities, thereby enabling more intact drugs to enter the intestine. It has also been found that CaP nanoparticles that are functionalized with chitosan or polyethylene glycol enhance further uptake of peptides by epithelial cells via transcellular and paracellular pathways.

CaP systems are also used in the delivery of antioxidants and hormones. Indicatively, CaP nanoparticles that are loaded with quercetin, vitamin E, and raloxifene have demonstrated remarkable stability and intestinal delivery, which presents prospects of actually managing chronic diseases orally [32] (Table 1). Raloxifene hydrochloride is a selective estrogen receptor modulator (SERM) with poor water solubility and high first-pass metabolism, which makes the oral bioavailability of the drug low (~2%). CaP nanoparticles have been developed as good carriers for oral delivery. Electrostatic binding of raloxifene with the negatively charged phosphate surface of CaP promotes the encapsulation of CaP. When administered, the nanoparticles keep raloxifene supersaturated in the lumen of the intestines, which enhances absorption. Comparative analysis has indicated that bioavailability has also increased nearly four times with the use of CaP nanoparticle formulations as compared to traditional pills. PEG or casein stabilizers used in the synthesis enhanced further dispersion, intestinal retention, and pharmacokinetic consistency.

Advantages and Limitations of Calcium Phosphate-Based Oral Drug Delivery Systems

The carriers made of calcium phosphate (CaP) have a combination of physicochemical and biological properties that render them highly suitable for the delivery of oral drugs. Their key strengths are that they are biocompatible, biodegradable, safe, pH responsive in terms of solubility and cost-efficient. As a mineral naturally occurring in the human body, CaP is by its nature, non-toxic and metabolically acceptable. When it is degraded, it releases calcium and phosphate ions; these are vital nutrients and hence long-term buildup or poisoning is prevented [33]. The second significant benefit is their pH-responsive dissolution characteristics that guarantee site-specific drug delivery. CaP is reasonably resistant to stomach acidity, and offers protection to acid-sensitive drugs, and is slowly soluble in intestinal conditions, resulting in controlled release and increased drug absorption. Also, surface chemistry can be engineered to CaP by doping or polymer coating to achieve released kinetics, as well as enhanced mucoadhesion. Its GRAS (Generally Recognized as Safe) regulatory status adds to its attractiveness to use as a pharmaceutical. As compared to polymeric carriers, including PLGA, chitosan and Eudragit, CaP systems are more thermostable, less immunogenic, and more compatible within a broad pH range. In addition, they do not experience the burst release that is commonly experienced in polymeric systems and ensure drug stability at the time of storage.

There are, however, some constraints. CaP nanoparticles are more likely to be aggregative in aqueous solutions, particularly under ionic conditions of physiological conditions, resulting in unreliable particle size and dispersion. Uncontrolled variability and consistency of particles in large-scale production is still production problem. Also, the low mechanical strength may limit the application of pure CaP formulations in compressing tablets without any mix with excipients. The other major limitation concerns the relatively slow dissolution of the crystalline CaP forms (e.g., HAp), which can restrict the use of the rapid drug release (e.g., injections) application [34]. Future studies are

Table 1: Representative examples of drugs delivered *via* calcium phosphate-based oral systems

Drug	*Type*	*Formulation type*	*Outcome*
Curcumin	Antioxidant	CaP nanoparticle	↑ Solubility (3.5×), ↑ Bioavailability
Paclitaxel	Anticancer	CaP nanocomposite	↑ Oral absorption, ↓ degradation
Insulin	Peptide hormone	CaP–chitosan hybrid nanoparticle	Protected against gastric pH, ↑ intestinal uptake
Raloxifene	Hormonal (SERM)	CaP–PEG nanoparticle	4× ↑ bioavailability, ↑ stability
Quercetin	Antioxidant	Biomimetic CaP nanoparticle	↑ Permeability and intestinal retention

addressing these shortcomings by surface functionalizing, polymer hybridizing and engineering particles to enhance stability, scalability and therapeutic efficacy. CaP systems are also a great compromise between safety and performance when optimized correctly, unlike traditional oral delivery carriers [35].

Future Perspectives

The history of the generation of calcium phosphate (CaP)-based micro- and nanoparticles as oral drug delivery systems is still an ongoing process due to the continuous advances in nanotechnology, material science and pharmaceutical engineering. Although existing literature has indicated that they have very good safety and effectiveness records, there are a few future areas that are of critical concern regarding clinical translation.

To begin with, upcoming studies should focus on *in-vivo* pharmacokinetic and pharmacodynamic studies in order to develop explicit associations between formulation design and treatment effects. The majority of studies that have been done are *in-vitro* or preclinical and do not have long-term safety and absorption data in human models. Such correlations will be developed and increase the acceptability of regulatory and facilitate product commercialization [36].

Second, another approach that is in the pipeline is the incorporation of multifunctional hybrid systems. The addition of CaP to biopolymers (e.g., chitosan, alginate, PEG) or lipids can enhance colloidal stability, mucosal adhesion and controlled release. The development of responsive material with smart properties, including enzyme- or microbiota-responsive CaP composites, can be used as the source of targeted release in target regions of the intestines. In addition, surface functionalization with peptides or ligands may promote receptor-based uptake of drugs that need specific sites of absorption. Lastly, scale-up and reproducibility are also major manufacturing issues. Continuous synthesis methods, including microfluidic precipitation and spray-based hybridization, are encouraging in the synthesis of particles of uniform size and morphology with strict control [37]. Computational modeling should also be incorporated in further studies in order to anticipate the kinetics of dissolution, release, and absorption to speed up rational formulation design.

CONCLUSION

It is observed that calcium phosphate (CaP)-micro and nanoparticle systems have become highly efficient, biocompatible, and versatile delivery systems of oral drugs. This is because of their physicochemical versatility, pH sensitivity, and ion-exchange capability, which can be used to precisely regulate drug release and absorption in the gastrointestinal tract. The CaP carriers are the only systems that combine the safety, stability and targeted dissolution to protect and enhance the delivery of poorly soluble and labile drugs in comparison to traditional polymeric or lipid-based systems. As this review shows, CaP nanoparticles enhance oral bioavailability via several mechanisms such as increased solubility, maintenance of supersaturation, mucosal adhesion and modulation of the microenvironment. Although there are limitations presently, e.g., aggregation, difficulty in scale up, variability in dissolution, etc, continued progress in hybridization, surface modification and process engineering is still breaking through these limitations.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Gupta R, Mishra B. Advances in oral drug delivery systems: Overcoming challenges of solubility and bioavailability. Eur J Pharm Biopharm. 2020;152:1–14.
2. Wu F, Ma Q, Tian G, Chen K, Yang R, Shen J. Formulation and evaluation of solid self-nanoemulsifying drug delivery system of cannabidiol for enhanced solubility and bioavailability. Pharmaceutics. 2025;17(3):340.
3. Servatan M, Mutlu P, Ertunç S, Sanaeifard S, Şahin B, Yilmazer-Hitit Z. Application of inorganic nanomaterials in transdermal and topical medications: Influential parameters, opportunities and challenges. Comments Inorg Chem. 2025;45(2):88–135.
4. Hong H, Ma W, Jiao Y, Cheng B, Yang J, Li B, *et al*. Synthesis and study of amorphous calcium phosphate dual-targeted drug-carrying platforms. J Mater Chem B. 2025;13(25):7463–7477.
5. Montesissa M, Tommasini V, Rubini K, Boi M, Baldini N, Boanini E. State of art and perspective of calcium phosphate-based coatings coupled with bioactive compounds for orthopedic applications. Nanomaterials (Basel). 2025;15(15):1199.
6. Popova VK, Pyshnyi DV, Dmitrienko EV. Biomedical applications of calcium carbonate nanoparticles: A review of recent advances. ACS Biomater Sci Eng. 2025;11(11):6359–6385.
7. Abozaid D, Azab A, Bahnsawy MA, Eldebawy M, Ayad A, Soomro R, *et al*. Bioactive restorative materials in dentistry: A comprehensive review of mechanisms, clinical applications, and future directions. Odontology. 2025 Aug. doi:10.1007/s10266-025-01162-w.
8. Sidorov ID, Oleynikova EI, Pudovkin MS, Nizamutdinov AS, Semashko VV, Gafurov MR, *et al*. Spectral and kinetic characteristics of precipitated and heat-treated hydroxyapatite and tricalcium phosphate doped with europium. Opt Mater. 2025;159:116609.
9. Garala K, Ughreja R, Ranpara R, Dholaria N. Optimizing bioavailability through natural excipients: A sustainable approach to drug delivery.

In: Innovative Pharmaceutical Excipients: Natural Sources. Singapore: Springer; 2025. p. 321–343. doi:10.1007/978-981-96-7959-1_13.
10. Gu X, Li Y, Qi C, Cai K. Biodegradable magnesium phosphates in biomedical applications. J Mater Chem B. 2022;10(13):2097–2112.
11. Liu L, Yao W, Rao Y, Lu X, Gao J. pH-responsive carriers for oral drug delivery: Challenges and opportunities of current platforms. Drug Deliv. 2017;24(1):569–581.
12. Onder AC, Tomak A, Karakus CO. Optimizing the dispersion of calcium phosphate nanoparticles for cellular studies using statistical design of experiments. Ceram Int. 2023;49(16):26890–26899.
13. Ito T, Otsuka M. Application of calcium phosphate as a controlled-release device. Biol Pharm Bull. 2013;36(11):1676–1682.
14. Cao P, Wang J, Sun B, Rewatkar P, Popat A, Fu C, *et al.* Enhanced mucosal transport of polysaccharide-calcium phosphate nanocomposites for oral vaccination. ACS Appl Bio Mater. 2021;4(11):7865–7878.
15. Victor SP, Sharma CP. Calcium phosphates as drug delivery systems. J Biomater Tissue Eng. 2012;2(4):269–279.
16. Cai Y, Tang R. Calcium phosphate nanoparticles in biomineralization and biomaterials. J Mater Chem. 2008;18:3775–3787.
17. Uskoković V, Uskoković DP. Nanosized hydroxyapatite and other calcium phosphates: Chemistry of formation and application as drug and gene delivery agents. J Biomed Mater Res B Appl Biomater. 2011;96(1):152–191.
18. Ishikawa K, Garskaite E, Kareiva A. Sol–gel synthesis of calcium phosphate-based biomaterials—A review of environmentally benign, simple, and effective synthesis routes. J Sol-Gel Sci Technol. 2020;94(3):551–572.
19. Le Grill S, Soulie J, Coppel Y, Roblin P, Lecante P, Marsan O, *et al.* Spray-drying-derived amorphous calcium phosphate: A multi-scale characterization. J Mater Sci. 2021;56(2):1189–1202.
20. Trofimov AD, Ivanova AA, Zyuzin MV, Timin AS. Porous inorganic carriers based on silica, calcium carbonate and calcium phosphate for controlled/modulated drug delivery: Fresh outlook and future perspectives. Pharmaceutics. 2018;10(4):167.
21. Zhang H, Yan D, Korale Gedara SM, Dingiri Marakkalage SF, Methlal JGK, Han Y, *et al.* Effects of crystallinity and surface modification of calcium phosphate nanoparticles on the loading and release of tetracycline hydrochloride. IOP Conf Ser Mater Sci Eng. 2017;182:012052.
22. Lv Y, Huang H, Yang B, Liu H, Li Y, Wang J. A robust pH-sensitive drug carrier: Aqueous micelles mineralized by calcium phosphate based on chitosan. Carbohydr Polym. 2014;111:101–107.
23. Sun H, Zhang C, Zhang B, Song P, Xu X, Gui X, *et al.* 3D printed calcium phosphate scaffolds with controlled release of osteogenic drugs for bone regeneration. Chem Eng J. 2022;427:130961.
24. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu Rev Biomed Eng. 2012;14:1–16.
25. Lee JA, Kim MK, Kim HM, Lee JK, Jeong J, Kim YR, *et al.* The fate of calcium carbonate nanoparticles administered by oral route: Absorption and their interaction with biological matrices. Int J Nanomedicine. 2015;10:2273–2293.
26. Yang Y, Zhu S, Guo W, Feng Y, Guo T, Wu H. Formation of calcium phosphate nanoparticles mediated by animal protein hydrolysates enhances calcium absorption by murine small intestine ex vivo. Food Funct. 2019;10(10):6666–6674.
27. Carmona FJ, Dal Sasso G, Bertolotti F, Ramírez-Rodríguez GB, Delgado-López JM, Pedersen JS, *et al.* The role of nanoparticle structure and morphology in the dissolution kinetics and nutrient release of nitrate-doped calcium phosphate nanofertilizers. Sci Rep. 2020;10(1):12396.
28. Kaneko K, Miyasaka R, Hayman R. Nano-hydroxyapatite improves intestinal absorption of acetazolamide (BCS Class IV drug)–but how? PLoS One. 2022;17(5):e0268067. doi:10.1371/journal.pone.0268067.
29. Cui X, Bao L, Wang X, Chen C. The nano-intestine interaction: Understanding the location-oriented effects of engineered nanomaterials in the intestine. Small. 2020;16(21):e1907665.
30. van Rijt S, de Groot K, Leeuwenburgh SCG. Calcium phosphate and silicate-based nanoparticles: History and emerging trends. Tissue Eng Part A. 2022;28(11–12):461–477.
31. Wu Q, Gao H, Vriesekoop F, Liu Z, He J, Liang H. Calcium phosphate coated core-shell protein nanocarriers: Robust stability, controlled release and enhanced anticancer activity for curcumin delivery. Mater Sci Eng C. 2020;115:111094.
32. Zhang ML, Cheng J, Xiao YC, Yin RF, Feng X. Raloxifene microsphere-embedded collagen/chitosan/β-tricalcium phosphate scaffold for effective bone tissue engineering. Int J Pharm. 2017;518(1–2):80–85.
33. Theiss F, Apelt D, Brand B, Kutter A, Zlinszky K, Bohner M, *et al.* Biocompatibility and resorption of a brushite calcium phosphate cement. Biomaterials. 2005;26(21):4383–4394.
34. Sokolova V, Epple M. Biological and medical applications of calcium phosphate nanoparticles. Chem Eur J. 2021;27(27):7471–7488.
35. Skrtic D, Antonucci JM, Eanes ED, Eichmiller FC, Schumacher GE. Physicochemical evaluation of bioactive polymeric composites based on hybrid amorphous calcium phosphates. J Biomed Mater Res. 2000;53(4):381–391.
36. Chai YC, Carlier A, Bolander J, Roberts SJ, Geris L, Schrooten J, *et al.* Current views on calcium phosphate osteogenicity and the translation into effective bone regeneration strategies. Acta Biomater. 2012;8(11):3876–3887.
37. Verma A, Sharma S, Gupta PK, Singh A, Teja BV, Dwivedi P, *et al.* Vitamin B12 functionalized layer by layer calcium phosphate nanoparticles: A mucoadhesive and pH-responsive carrier for improved oral delivery of insulin. Acta Biomater. 2016;31:288–300.

HOW TO CITE THIS ARTICLE: Patel MA, Soni TG. Calcium Phosphate Based Micro and Nanoparticles in Oral Drug Delivery: Formulation Approaches, Intestinal Fate, and Bioavailability Enhancement: A Review. *J Adv Sci Res*. 2026;17(3): 29-35 **DOI:** 10.55218/JASR.2026170305