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CHARACTERIZATION, PHARMACEUTICAL APPLICATIONS, CONVENTIONAL AND NOVEL DRUG DELIVERY SYSTEMS — A COMPREHENSIVE REVIEW

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ABSTRACT

Calcium carbonate ($CaCO_3$) is one of the most extensively utilized inorganic compounds in pharmaceutical, food, and biomedical sciences. Among its diverse natural sources, chicken eggshells have emerged as a highly sustainable, cost-effective, and biocompatible raw material for $CaCO_3$ extraction. Eggshell-derived calcium carbonate (ES-$CaCO_3$) constitutes approximately 94–96% of the eggshell composition and offers several physicochemical advantages over synthetically produced or commercially mined calcium carbonate, including superior crystalline quality, minimal heavy metal contamination, and excellent biocompatibility. This review comprehensively examines the extraction, purification, and physicochemical characterization of ES-$CaCO_3$, including analysis by X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and thermogravimetric analysis (TGA). The biological and pharmacological properties of ES-$CaCO_3$ are detailed, encompassing its antacid activity, calcium supplementation efficacy, bone regeneration potential, and antimicrobial properties. The review further explores five pharmaceutical formulation approaches: three conventional systems (tablets, capsules, and oral suspensions) and two novel drug delivery systems (medicated chewing gum and floating gastroretentive tablets) wherein ES-$CaCO_3$ serves as either an active ingredient or a multifunctional excipient. Additionally, the role of ES-$CaCO_3$ in environmental applications and biowaste valorization is discussed. The discussion section addresses current challenges, regulatory considerations, clinical evidence, and comparative performance of ES-$CaCO_3$ versus commercial-grade $CaCO_3$. Finally, future research directions focusing on nanoparticle synthesis, targeted drug delivery, and industrial scalability are outlined.

KEYWORDS: Eggshell; Calcium carbonate; Pharmaceutical formulation; Biowaste valorization; Medicated chewing gum; Gastroretentive drug delivery; Calcium supplementation; Bone regeneration; Green chemistry; Novel drug delivery systems.

1. INTRODUCTION

The global pharmaceutical industry continuously seeks natural, sustainable, and cost-effective raw materials that can serve both as active pharmaceutical ingredients (APIs) and as multifunctional excipients. Calcium carbonate ($CaCO_3$), with its Chemical Abstracts Service (CAS) registry number 471-34-1, is a versatile inorganic salt that has been listed in numerous pharmacopoeias worldwide, including the United States Pharmacopoeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), and Indian Pharmacopoeia (IP). Its applications span antacid therapy, calcium supplementation, direct compression tablet excipient, and a pH-adjusting agent in various formulations.

Globally, approximately 70 to 80 million metric tons of eggs are produced annually, generating an enormous quantity of eggshell waste. In India alone, poultry

production generates millions of tons of eggshell waste yearly, most of which is discarded in landfills, contributing to environmental pollution and resource wastage. Each eggshell weighs approximately 5 to 6 grams and constitutes nearly 10–11% of the total egg weight. Chemically, eggshells are composed predominantly of calcite-phase $CaCO_3$ (94–96%), along with magnesium carbonate (1%), calcium phosphate (1%), and organic matter including proteins such as osteopontin and lysozyme embedded in the shell matrix.

The extraction and repurposing of $CaCO_3$ from eggshells represents an outstanding example of circular economy and green chemistry principles. Unlike mined limestone or synthetic precipitated calcium carbonate (PCC), ES-$CaCO_3$ is produced from biowaste, thereby reducing the carbon footprint of pharmaceutical manufacturing. Several studies have demonstrated that ES-$CaCO_3$ is pharmacologically comparable or even superior to commercial $CaCO_3$ due to its naturally occurring trace minerals (magnesium, strontium, fluoride), its high surface area, and its excellent compressibility profile.
The significance of eggshell-derived $CaCO_3$ in drug delivery has grown considerably in the last two decades. Researchers have explored its utility in both conventional formulations such as tablets, capsules, and suspensions, and in novel drug delivery systems (NDDS) such as medicated chewing gums, floating drug delivery systems, mucoadhesive systems, transdermal patches, and nanoparticulate carriers. The ability of $CaCO_3$ to act simultaneously as an active ingredient and a functional excipient makes it uniquely attractive for pharmaceutical innovation.

This review aims to consolidate current knowledge on eggshell-derived $CaCO_3$ by critically examining: (i) the composition and structure of eggshells; (ii) extraction and characterization methods; (iii) pharmacological and biological activities; (iv) applications in five formulation categories; (v) a comparative discussion with commercial-grade $CaCO_3$; and (vi) future research directions. By providing this comprehensive overview, the review aims to guide pharmaceutical scientists, formulation researchers, and policymakers toward more sustainable and clinically effective use of this underutilized bioresource.

2. EGGSHELL COMPOSITION AND STRUCTURE

2.1 Macrostructure and Layers of the Eggshell

The avian eggshell is a complex, hierarchically organized bioceramic structure that has evolved to protect the developing embryo while permitting gas exchange. It consists of multiple distinct layers, each with a specific composition and function. The innermost layer is the shell membrane, a double-layered fibrous protein network primarily composed of type I and V collagens, fibronectin, osteopontin, and lysozyme. This membrane, approximately 60–70 micrometers thick, serves as the scaffold upon which mineral deposition occurs.

Overlying the shell membranes is the mammillary layer, the innermost mineralized stratum, composed of spherical calcite cones anchored to the outer shell membrane. These mammillary knobs serve as nucleation sites for crystal growth. The palisade (or columnar) layer, comprising the bulk of the shell thickness (approximately 300–400 μm), consists of elongated calcite columns oriented perpendicular to the shell surface. This layer contains pores (pore canals) that allow gas exchange between the embryo and external environment. The outermost layer is the cuticle, a thin proteinaceous coating of amorphous $CaCO_3$ and polysaccharides that protects against microbial invasion and regulates gas and water vapor permeability.

2.2 Chemical Composition

The chemical composition of a typical chicken eggshell is as follows: calcium carbonate ($CaCO_3$): 94–96% (predominantly calcite polymorph); magnesium carbonate ($MgCO_3$): 0.8–1.2%; calcium phosphate ($Ca_3(PO_4)_2$): 0.8–1.0%; organic matter (proteins, glycoproteins): 2–3%; trace elements including strontium (Sr), barium (Ba), zinc (Zn), fluoride (F^-), and silicon (Si). The presence of these trace elements in physiologically relevant concentrations is one factor that distinguishes ES-$CaCO_3$ from synthetic PCC, which typically lacks such mineral diversity.

2.3 Polymorphic Forms of Calcium Carbonate in Eggshells

Calcium carbonate exists in three anhydrous crystalline polymorphs: calcite (rhombohedral), aragonite (orthorhombic), and vaterite (hexagonal), as well as two hydrated forms: monohydrocalcite and ikaite. Eggshell $CaCO_3$ is predominantly in the calcite form, which is the thermodynamically most stable polymorph under ambient conditions. X-ray diffraction analysis of eggshells consistently reveals characteristic calcite diffraction peaks at 2θ values of approximately 23.1°, 29.4°, 31.5°, 36.0°, 39.4°, 43.2°, 47.1°, and 48.5°. The predominance of calcite in ES-$CaCO_3$ is significant because calcite exhibits lower solubility ($K_{sp} = 3.4 \times 10^{-9}$) compared to aragonite ($K_{sp} = 6.0 \times 10^{-9}$), which has implications for its dissolution profile in pharmaceutical formulations.

3. EXTRACTION, PROCESSING, AND CHARACTERIZATION OF EGGSHELL-DERIVED $CaCO_3$

3.1 Collection and Pre-treatment of Eggshells

The first step in obtaining pharmaceutical-grade ES-$CaCO_3$ is the collection and pre-treatment of raw eggshells. Eggshells are collected from food processing industries, bakeries, and institutional kitchens to ensure a consistent supply. The shells must be cleaned thoroughly to remove adhering albumen (egg white), which can introduce protein contamination into the final product. The standard pre-treatment protocol involves: (i) washing with warm water (40–50°C) to remove gross

contamination; (ii) boiling at 100°C for 15–20 minutes to denature and loosen residual proteins; (iii) removal of the inner shell membrane by mechanical peeling or by incubating in a dilute sodium hydroxide solution (0.5 M NaOH) for 30 minutes; (iv) rinsing with distilled water to neutrality; and (v) drying at 105°C for 2–4 hours.

The removal of the shell membrane is a critical step because the membrane contains proteins and other organic molecules that, if retained, can affect the purity and chemical properties of the extracted $CaCO_3$. Studies have shown that incomplete membrane removal leads to elevated nitrogen content in the final product, which is unacceptable for pharmaceutical applications.

3.2 Calcination and Powder Preparation

Following drying, the cleaned eggshells are ground using a ball mill or mortar and pestle into a coarse powder. For certain applications, the powder undergoes calcination at temperatures ranging from 800°C to 1000°C in a muffle furnace. At these temperatures, $CaCO_3$ decomposes to calcium oxide (CaO) and carbon dioxide (CO_2). The resulting CaO can be subsequently hydrated to calcium hydroxide ($Ca(OH)_2$) or re-carbonated to regenerate high-purity $CaCO_3$ through controlled CO_2 bubbling. However, for direct pharmaceutical use where the calcite structure is desired, calcination is often avoided, and the powder is simply milled to the target particle size and sieved.

3.3 Physicochemical Characterization

3.3.1 X-ray Diffraction (XRD)

XRD is the primary technique for confirming the crystalline identity and phase purity of ES-$CaCO_3$. The diffractograms of eggshell powder consistently show characteristic calcite peaks without the presence of aragonite or vaterite peaks, confirming phase purity. The degree of crystallinity, calculated from XRD data using the Scherrer equation, typically ranges from 85 to 95% for well-processed ES-$CaCO_3$, which is comparable to commercial grades.

3.3.2 Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy provides information on the functional groups and molecular bonding in ES-$CaCO_3$. Characteristic absorption bands for calcite appear at approximately 712 cm^{-1} (ν_4 in-plane bending), 876 cm^{-1} (ν_2 out-of-plane bending), and 1397–1420 cm^{-1} (ν_3 asymmetric stretching of CO_3^{2-}). The absence of strong amide bands (around 1650 cm^{-1} and 3300 cm^{-1}) in properly processed samples confirms effective protein removal.

3.3.3 Scanning Electron Microscopy (SEM) and Particle Size Analysis

SEM reveals the morphology of ES-$CaCO_3$ particles, typically showing irregular, angular morphologies with rough surfaces after milling. The BET surface area of milled ES-$CaCO_3$ ranges from 1 to 10 m^2/g depending on the milling conditions. Particle size distribution, measured by laser diffraction, is an important quality attribute for pharmaceutical applications: fine-milled ES-$CaCO_3$ with a D90 of less than 50 μm is suitable for direct compression tablets, while coarser particles (D90 > 100 μm) are appropriate for suspension formulations.

3.3.4 Thermogravimetric Analysis (TGA)

TGA reveals the thermal decomposition profile of ES-$CaCO_3$. A single major decomposition event occurs between 600°C and 900°C, corresponding to the thermal decomposition of $CaCO_3$ to CaO and CO_2. The residual mass after complete decomposition corresponds to CaO, from which the $CaCO_3$ purity can be calculated. High-purity ES-$CaCO_3$ shows a $CaCO_3$ content of ≥99% after proper processing, meeting pharmacopoeial standards.

3.3.5 Atomic Absorption Spectroscopy (AAS) for Heavy Metal Content

Pharmacopoeial specifications for $CaCO_3$ require stringent limits on heavy metals including lead (<3 ppm), arsenic (<2 ppm), mercury (<1 ppm), and cadmium (<1 ppm). Multiple studies have confirmed that properly processed ES-$CaCO_3$ meets these specifications, with heavy metal levels significantly lower than those found in some mined limestone-derived $CaCO_3$ products. This low heavy metal burden is a key safety advantage of ES-$CaCO_3$.

4. PHARMACOLOGICAL AND BIOLOGICAL ACTIVITIES OF ES-$CaCO_3$

4.1 Antacid Activity

Calcium carbonate is one of the most potent and rapidly acting antacids available. Its mechanism of action involves direct chemical neutralization of gastric hydrochloric acid (HCl) according to the reaction: $CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$. The acid-neutralizing capacity (ANC) of ES-$CaCO_3$, determined by the USP method, is approximately 0.92–0.98 mmol HCl/mg, which is comparable to pharmaceutical-grade $CaCO_3$ (ANC = 0.95–0.99 mmol HCl/mg). In vitro studies comparing ES-$CaCO_3$ with commercial antacid-grade $CaCO_3$ have found no statistically significant difference in neutralization kinetics, supporting the suitability of ES-$CaCO_3$ as an antacid active ingredient.

Unlike sodium bicarbonate (which causes systemic alkalosis and carbon dioxide-mediated acid rebound) and aluminum/magnesium hydroxide (which require large doses and cause constipation or diarrhea), $CaCO_3$-based antacids offer a balanced profile. The CO_2 released during neutralization can cause belching, which is the most common side effect. ES-$CaCO_3$, being essentially equivalent in chemical composition to pharmaceutical $CaCO_3$, shares this side effect profile.

4.2 Calcium Supplementation and Bioavailability

Calcium deficiency is a global public health concern associated with osteoporosis, rickets, osteomalacia, dental caries, muscle cramps, and cardiovascular

dysrhythmias. The World Health Organization (WHO) recommends a daily calcium intake of 1000–1200 mg for adults, with higher requirements during pregnancy, lactation, adolescence, and post-menopause. $CaCO_3$ is the most widely used calcium supplement due to its high elemental calcium content (40% by weight), compared to calcium citrate (21%), calcium gluconate (9%), and calcium lactate (13%).

The bioavailability of calcium from ES-$CaCO_3$ has been evaluated in several animal studies. A study by Schaafsma et al. (1999) demonstrated that calcium from eggshell powder was absorbed significantly better than calcium from calcium carbonate tablets in ovariectomized rats, a model of postmenopausal osteoporosis. The authors attributed this enhanced bioavailability to the presence of trace elements and the organic matrix remnants in eggshell powder, which may facilitate intestinal calcium transport. Further human studies have confirmed that ES-$CaCO_3$ supplementation effectively increases serum calcium levels and reduces markers of bone resorption.

4.3 Bone Regeneration and Osteoconductive Properties

ES-$CaCO_3$ has demonstrated considerable promise as a bone graft substitute and scaffold material in both in vitro and in vivo studies. The rationale for its use in bone regeneration stems from the chemical similarity between $CaCO_3$ and the inorganic components of bone (hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$), and from its osteoconductive properties. In vivo animal studies using critical-size bone defect models in rats, rabbits, and dogs have shown that eggshell-derived $CaCO_3$ granules support bone ingrowth and gradual resorption with concurrent new bone formation.

The osteogenic potential of ES-$CaCO_3$ has been further enhanced by combining it with collagen, hydroxyapatite, or growth factors such as bone morphogenetic protein-2 (BMP-2). Such composites show superior bone regeneration compared to ES-$CaCO_3$ alone, suggesting synergistic interactions. The controlled degradation of $CaCO_3$ in the physiological environment provides a sustained local source of calcium ions, which promote osteoblast differentiation and mineralization.

4.4 Antimicrobial Properties

Both eggshell powder and its calcined derivative (CaO) have demonstrated antimicrobial activity against a range of pathogenic microorganisms. The antimicrobial mechanism of CaO involves the generation of highly alkaline conditions (pH > 12) upon hydration, which denatures bacterial proteins and disrupts cell membranes. ES-$CaCO_3$ itself is reported to have mild antimicrobial activity against Escherichia coli, Staphylococcus aureus, and Candida albicans in agar diffusion assays, possibly related to the alkaline microenvironment it creates and the presence of lysozyme residues from the eggshell membrane.

4.5 Phosphate Binding and Hyperphosphatemia Management

In patients with chronic kidney disease (CKD), elevated serum phosphate (hyperphosphatemia) is a significant risk factor for cardiovascular mortality. Calcium carbonate is used as a phosphate binder, where it reacts with dietary phosphate in the gastrointestinal tract to form insoluble calcium phosphate, reducing phosphate absorption. ES-$CaCO_3$ has been evaluated as a phosphate binder in CKD patients and has shown comparable efficacy to pharmaceutical-grade $CaCO_3$ while offering a more economical and sustainable alternative.

5. PHARMACEUTICAL FORMULATIONS OF ES-$CaCO_3$

Eggshell-derived calcium carbonate has been investigated in a wide variety of pharmaceutical dosage forms. In this section, five representative formulation categories are reviewed in detail: three conventional formulations (tablets, capsules, and oral suspensions) and two novel drug delivery systems (medicated chewing gum and floating gastroretentive tablets).

Table 1: Summary of pharmaceutical formulation categories employing ES-$CaCO_3$, their roles, advantages, and challenges.

Formulation Type	Role of ES-$CaCO_3$	Key Advantages	Challenges
Tablets (Conventional)	Direct compression diluent, API (antacid/Ca supplement), pH modifier	High dose capacity, patient compliance	Gritty mouthfeel, coating required for taste masking
Capsules (Hard Gelatin)	API filler, moisture scavenger, anti-caking agent	Ease of formulation, avoids compression	Segregation, hygroscopicity of blends
Oral Suspension	Active antacid agent, suspending vehicle component	Suitable for dysphagia patients, rapid onset	Settling, pH stability, palatability
Medicated Chewing Gum	API (Ca supplement/antacid), gum base filler, sweetener synergist	Novel delivery, buccal absorption, patient-friendly	Uniform drug distribution in gum matrix, release control
Floating Gastroretentive Tablet	CO_2 generator for buoyancy, API, matrix former	Prolonged gastric residence, sustained Ca release	Requires acidic gastric pH, posture-dependent

5.1 Conventional Formulation I: Calcium Carbonate Tablets

5.1.1 Overview and Rationale

Tablets are the most widely prescribed and manufactured pharmaceutical dosage form globally, accounting for approximately 70–80% of all solid oral dosage forms. $CaCO_3$ tablets represent one of the largest volume tablet products in the world, used as antacids (e.g., Tums®, Digene®) and calcium supplements (Os-Cal®, Calci-Mix®). The substitution of pharmaceutical-grade $CaCO_3$ with ES-$CaCO_3$ in tablet formulations has been the focus of numerous studies, motivated by economic and environmental sustainability considerations.

5.1.2 Formulation Composition and Design

A typical ES-$CaCO_3$ antacid tablet formulation contains: ES-$CaCO_3$ (500–1000 mg, active), microcrystalline cellulose (MCC, 50–100 mg, diluent/binder), croscarmellose sodium (15–25 mg, disintegrant), magnesium stearate (5–10 mg, lubricant), colloidal silicon dioxide (10 mg, glidant), peppermint flavor (5 mg), and saccharin sodium (2–3 mg, sweetener). ES-$CaCO_3$ is particularly amenable to direct compression due to its adequate compressibility index (Carr's index < 15%) and Hausner ratio (<1.18) when properly milled and classified.

5.1.3 Manufacturing Process

The manufacturing process for ES-$CaCO_3$ tablets involves: (i) milling and sieving of ES-$CaCO_3$ to the appropriate particle size (typically 44–180 µm for direct compression); (ii) blending with MCC and glidant in a tumble blender for 15 minutes; (iii) addition of lubricant and further blending for 3–5 minutes; (iv) compression on a rotary tablet press to a target hardness of 8–12 kp; (v) optional film coating with hydroxypropyl methylcellulose (HPMC) or enteric coating with Eudragit® L100 for taste masking or targeted release.

5.1.4 Quality Attributes and Performance

Studies evaluating ES-$CaCO_3$ tablets have demonstrated compliance with pharmacopoeial specifications: weight variation (±5%), tablet hardness (8–12 kp), friability (<1%), disintegration time (<15 minutes for uncoated tablets), and dissolution (≥75% of labeled $CaCO_3$ dissolved in 0.1 N HCl within 30 minutes, USP method). The acid-neutralizing capacity of ES-$CaCO_3$ tablets has been found equivalent to commercial antacid tablets in in vitro studies.

5.2 Conventional Formulation II: Hard Gelatin Capsules

5.2.1 Overview and Rationale

Hard gelatin capsules filled with calcium carbonate powder represent another widely employed conventional dosage form for calcium supplementation. Capsule formulations are particularly advantageous when: (i) the API cannot withstand compression forces; (ii) the dose is too high for a single tablet; (iii) a combination of APIs with incompatible compressibility profiles must be co-formulated; or (iv) rapid manufacturing turnaround is required without significant equipment investment. ES-$CaCO_3$ is an ideal capsule fill material due to its free-flowing powder characteristics after appropriate milling and lubrication.

5.2.2 Formulation Design

A representative ES-$CaCO_3$ capsule formulation for calcium supplementation contains: ES-$CaCO_3$ (500 mg, active ingredient providing approximately 200 mg elemental calcium per capsule), dicalcium phosphate (50 mg, diluent), colloidal silicon dioxide (10 mg, glidant), and magnesium stearate (5 mg, lubricant). The formulation is typically filled into size 0 or size 00 hard gelatin capsules to accommodate the required dose. Vegetarian capsules (hydroxypropyl methylcellulose, HPMC) are increasingly preferred for consumer products targeting vegetarian and vegan populations.

5.2.3 Role of ES-$CaCO_3$ as a Moisture Scavenger

An interesting secondary role of ES-$CaCO_3$ in capsule formulations is its ability to adsorb moisture, thereby protecting co-encapsulated moisture-sensitive APIs (e.g., aspirin, pantoprazole) from degradation. This moisture-scavenging property is related to the hygroscopic nature of $CaCO_3$ and its large surface area. Studies have confirmed that the inclusion of ES-$CaCO_3$ in capsule blends containing moisture-sensitive drugs reduces drug degradation rates during accelerated stability testing (40°C/75% relative humidity, 6 months) compared to formulations without the calcium salt.

5.2.4 Dissolution and Bioavailability

The dissolution of $CaCO_3$ from capsules is influenced by the gastric pH, particle size, and the presence of food. Under fasting conditions (gastric pH 1.5–2.0), dissolution is rapid and complete within 15–20 minutes. Under fed conditions (gastric pH 4.0–6.0), dissolution may be slower, but the food matrix itself provides an acidic environment that promotes dissolution.

5.3 Conventional Formulation III: Oral Suspension

5.3.1 Overview and Rationale

Oral suspensions represent the preferred liquid dosage form for calcium carbonate administration in pediatric and geriatric populations, as well as in patients with dysphagia. The insolubility of $CaCO_3$ in water necessitates its formulation as a suspension rather than a solution. $CaCO_3$ suspensions are among the most widely used antacid liquid formulations globally (e.g., Milk of Magnesia blends, Gaviscon® liquid). The substitution of pharmaceutical-grade $CaCO_3$ with ES-$CaCO_3$ in suspension formulations has been demonstrated to be feasible with appropriate particle size control and formulation optimization.

5.3.2 Formulation Composition

A representative ES-$CaCO_3$ oral antacid suspension contains: ES-$CaCO_3$ (40–50 mg/mL suspension, equivalent to 200–250 mg/5 mL dose), carboxymethyl cellulose sodium (CMC-Na, 0.5–1.0%, w/v, suspending agent), sorbitol (20–30%, w/v, sweetener and viscosity enhancer), sodium benzoate (0.1%, w/v, preservative), peppermint oil (0.05%, v/v, flavoring agent), and purified water to volume. The pH of the suspension is adjusted to 6.5–7.5 to prevent particle agglomeration while maintaining chemical stability.

5.3.3 Stability Considerations

The key stability challenges for ES-$CaCO_3$ suspensions are sedimentation, particle size growth (Ostwald ripening), and microbial contamination. Sedimentation is controlled by optimizing the viscosity of the suspending medium using CMC-Na or xanthan gum, and by reducing particle size to below 20 µm to promote Brownian motion. Redispersibility, measured as the time and shaking effort required to re-homogenize the settled cake, should be acceptable (easy redispersion within 10 shaking cycles). The inclusion of electrolytes (e.g., sodium chloride 0.1%) in the formulation can reduce the electric double layer repulsion between particles and aid redispersion.

5.4 Novel Drug Delivery System I: Medicated Chewing Gum (MCG)

5.4.1 Background and Concept

Medicated chewing gum (MCG) is an innovative drug delivery platform that has gained regulatory recognition (Ph. Eur. monograph 0168; USP <3>) as a pharmaceutical dosage form. MCG delivers drugs via two primary routes: (i) buccal/oromucosal absorption during chewing, which avoids first-pass metabolism; and (ii) gastrointestinal absorption following swallowing of dissolved drug in saliva. MCG offers several advantages including patient-friendly administration (no water required), improved compliance in pediatric and geriatric patients, pleasant organoleptic properties, portability, and the ability to mask bitter drug tastes through the flavor system.

ES-$CaCO_3$ is a particularly well-suited active ingredient for MCG formulations because: (i) its antacid and calcium-supplementing effects benefit from rapid buccal delivery; (ii) its plasticity and particle size are compatible with gum base incorporation; (iii) its alkaline nature neutralizes oral acids, providing simultaneous dental protection; and (iv) it does not degrade under the mechanical and thermal stresses of MCG manufacturing.

5.4.2 Gum Base and Formulation Components

MCG for ES-$CaCO_3$ delivery consists of: gum base (25–30%, the non-digestible, insoluble matrix comprising elastomers such as polyvinyl acetate, polyisobutylene, and natural resins; resin esters; fillers; emulsifiers); ES-$CaCO_3$ (15–25%, active ingredient); sorbitol (30–40%, bulking sweetener and plasticizer); xylitol (5–10%, sweetener with additional dental benefits); glycerin (2–3%, humectant); peppermint or spearmint oil (0.5–1.0%, flavoring agent); lecithin (0.5%, emulsifier); and a softener (hydrogenated coconut oil, 1–3%).

5.4.3 Manufacturing Process

MCG is manufactured using a specialized chewing gum manufacturing line. The process involves: (i) melting of gum base at 60–80°C; (ii) addition of ES-$CaCO_3$ and gradual incorporation of sweeteners and plasticizers under continuous kneading; (iii) addition of flavors, colors, and remaining excipients; (iv) kneading to homogeneity at 40–60°C; (v) forming into pellets or slabs using conditioning and pressing machinery; (vi) scoring into individual gum pieces; and (vii) coating with a sugar-free coating (film coating with sorbitol or xylitol syrup). The residence temperature must be carefully controlled because excessive heat can lead to loss of volatile flavoring agents and potential degradation of heat-labile excipients.

5.4.4 Drug Release Mechanism and In Vitro Testing

Drug release from MCG is governed by the European Pharmacopoeia chewing apparatus method, which subjects the gum to simulated mastication (37°C, simulated saliva fluid or phosphate buffer pH 6.8, at a defined chewing rate). ES-$CaCO_3$ is released from the gum matrix as chewing progressively breaks down the gum structure and exposes the drug particles to the aqueous environment. Studies have demonstrated that 70–85% of ES-$CaCO_3$ can be released from optimized MCG formulations within 30 minutes of simulated chewing. The released $CaCO_3$ dissolves in oral saliva and gastric secretions, exerting antacid and supplementation effects.

5.4.5 Clinical Significance and Dental Benefits

A unique advantage of ES-$CaCO_3$ MCG over conventional antacid tablets is its dental protective effect. The alkaline environment created by dissolved $CaCO_3$ in saliva neutralizes oral acids produced by cariogenic bacteria (particularly Streptococcus mutans), thereby raising plaque pH above the critical level for enamel demineralization (pH < 5.5). Additionally, the mechanical action of chewing stimulates salivary flow, further diluting oral acids and providing buffering capacity. The combination of ES-$CaCO_3$ with xylitol in MCG represents a powerful anti-caries formulation approach, as xylitol has independently established anti-cariogenic activity through inhibition of bacterial fermentation.

5.5 Novel Drug Delivery System II: Floating Gastroretentive Tablets

5.5.1 Concept and Significance

Gastroretentive drug delivery systems (GRDDS) are engineered to prolong the residence time of dosage forms in the stomach, enabling sustained drug release and enhanced bioavailability for drugs with narrow absorption windows in the upper gastrointestinal tract. Floating drug delivery systems (FDDS) are among the

most widely studied GRDDS; they reduce in vivo bulk density to below that of gastric fluid (approximately 1.004 g/mL) and thereby float on the gastric contents, prolonging gastric residence from the typical 1–3 hours to 8–12 hours.

ES-$CaCO_3$ plays a dual role in floating tablet systems: (i) as an active ingredient (antacid or calcium supplement), its sustained release over an extended gastric residence period is pharmacokinetically advantageous; and (ii) as a CO_2 generator, it reacts with acidic citric or tartaric acid incorporated in the formulation to generate CO_2 gas, which becomes entrapped in the hydrated polymer matrix, imparting buoyancy. This dual functionality makes ES-$CaCO_3$ uniquely valuable in FDDS design.

5.5.2 Formulation Components

A representative ES-$CaCO_3$ floating tablet formulation contains: ES-$CaCO_3$ (500 mg, active + gas generator), hydroxypropyl methylcellulose K100M (HPMC K100M, 150 mg, rate-controlling hydrophilic matrix polymer), sodium alginate (50 mg, viscosity enhancer), citric acid (100 mg, effervescent acid), ethyl cellulose (30 mg, hydrophobic matrix component), magnesium stearate (10 mg, lubricant), and talc (10 mg, glidant). The HPMC-to-acid ratio is the most critical formulation variable controlling both floating performance and drug release rate.

5.5.3 Floating Mechanism and In Vitro Evaluation

Upon contact with simulated gastric fluid (SGF, pH 1.2, 37°C), HPMC hydrates rapidly to form a viscous gel layer around the tablet. Simultaneously, citric acid protonates (or reacts with the surrounding acidic medium), generating CO_2 that reacts with ES-$CaCO_3$ according to: $CaCO_3 + 2HCl$ (or $H_2C_6H_7O_7$) $\rightarrow CO_2 + CaCl_2 + H_2O$. The generated CO_2 becomes entrapped in the swelling HPMC matrix, creating a low-density, buoyant dosage form. The tablet floats within 1–5 minutes (floating lag time, FLT) and maintains buoyancy for 8–12 hours in optimized formulations.

Drug release from floating tablets follows a combination of diffusion (Fickian or anomalous) and erosion mechanisms. Release profiles fitted to the Korsmeyer-Peppas model typically show n values between 0.5 and 0.89, indicating anomalous (non-Fickian) transport. Zero-order release ($n \approx 1.0$) is achievable by incorporating hydrophobic polymers such as ethyl cellulose alongside HPMC. The extended release of calcium from floating tablets results in prolonged elevation of serum calcium levels compared to conventional immediate-release formulations.

6. OTHER PHARMACEUTICAL AND BIOMEDICAL APPLICATIONS OF ES-$CaCO_3$

6.1 Transdermal Formulations

Microparticulate ES-$CaCO_3$ has been explored as a physical penetration enhancer in transdermal drug delivery systems. When incorporated into gel or cream formulations, $CaCO_3$ microparticles can disrupt the stratum corneum lipid bilayer arrangement through physical abrasion, increasing skin permeability for co-formulated hydrophilic drugs. Studies with diclofenac sodium transdermal gel incorporating ES-$CaCO_3$ microparticles showed significantly enhanced permeation flux compared to formulations without $CaCO_3$. Additionally, ES-$CaCO_3$ can act as a pH-adjusting agent in topical formulations, creating an alkaline microenvironment that promotes the ionized form of weakly acidic drugs within the skin layers.

6.2 Nanoparticulate Drug Delivery

Nano-sized $CaCO_3$ particles (50–300 nm) derived from eggshells through wet precipitation methods have been investigated as pH-responsive drug delivery vehicles for intracellular drug delivery, particularly for anticancer applications. $CaCO_3$ nanoparticles dissolve rapidly at the slightly acidic pH of tumor microenvironments (pH 6.4–6.8) and endolysosomes (pH 4.5–5.5), enabling triggered release of encapsulated chemotherapeutic agents (e.g., doxorubicin, curcumin). The nanoparticles can be surface-modified with polyethylene glycol (PEG), folic acid, or other targeting ligands to enhance tumor-selective accumulation through the enhanced permeability and retention (EPR) effect and receptor-mediated endocytosis.

6.3 Dental Applications

ES-$CaCO_3$ has been incorporated into toothpaste and tooth powder formulations as a mild abrasive, calcium-donating agent, and whitening agent. Its Mohs hardness (approximately 3), moderate abrasivity, and chemical compatibility with fluoride make it suitable for dentifrice formulations. Clinical studies have demonstrated that toothpastes containing ES-$CaCO_3$ achieve similar plaque removal efficacy to commercially used calcium carbonate abrasives and provide supplementary remineralization effects on early carious lesions.

7. COMPARATIVE ANALYSIS: ES-$CaCO_3$ VERSUS COMMERCIAL $CaCO_3$

Table 2: Comparative analysis of key parameters between ES-$CaCO_3$ and commercially available $CaCO_3$.

Parameter	Eggshell-Derived $CaCO_3$	Commercial (Synthetic/Mined) $CaCO_3$
Source	Biowaste (poultry eggshells)	Limestone mining / chemical precipitation
Purity (%)	94–99% $CaCO_3$	99–99.9% $CaCO_3$ (PCC)
Crystal Form	Predominantly calcite	Calcite, aragonite, or vaterite (depending on process)
Trace Minerals	Mg, Sr, F, Zn, Si (naturally present)	Generally absent (synthetic); variable (mined)
Heavy Metals	Very low (well within pharmacopoeial	Variable; some mined sources may exceed limits

	limits)	
Bioavailability	Comparable or superior (animal models)	Standard reference
Compressibility	Good (Carr's index 12–18%)	Good to excellent (PCC: 8–15%)
Cost	Lower (biowaste feedstock)	Moderate to high (mining / synthetic costs)
Sustainability	Excellent (biowaste valorization)	Poor to moderate (mining impact)
Regulatory Status	Acceptable if purity/specification met	Fully established; listed in all major pharmacopoeias

8. DISCUSSION

The comprehensive body of literature reviewed in this paper provides compelling evidence that eggshell-derived calcium carbonate is not merely an alternative to synthetic or mined $CaCO_3$, but a biologically and pharmacologically distinctive material with unique advantages arising from its natural origin, chemical composition, and structural properties. The discussion that follows synthesizes findings across formulation categories, highlights key challenges, and identifies opportunities for advancement.

8.1 Pharmaceutical Quality and Regulatory Considerations

A consistent finding across multiple studies is that properly processed ES-$CaCO_3$ meets the quality specifications laid out in the USP, BP, and IP monographs for calcium carbonate. Parameters including assay (98–102% $CaCO_3$), heavy metals, acid-insoluble substances, loss on drying, and particle size distribution are all within acceptable limits when appropriate extraction and purification procedures are followed. This is critical for regulatory acceptance, as any deviation from pharmacopoeial standards would necessitate extensive quality justification and potentially slow regulatory approval timelines.

However, a significant regulatory gap exists: no major pharmacopoeia currently has a dedicated monograph for "eggshell-derived calcium carbonate" as a distinct pharmaceutical ingredient. Manufacturers wishing to use ES-$CaCO_3$ must therefore demonstrate equivalence to the existing $CaCO_3$ monograph through comprehensive characterization and qualification studies. The development of pharmacopoeial guidance specific to ES-$CaCO_3$ would substantially accelerate its adoption in pharmaceutical manufacturing.

8.2 Bioavailability and Clinical Evidence

The bioavailability evidence for ES-$CaCO_3$ is promising but not fully conclusive for all clinical scenarios. Animal studies have consistently shown comparable or superior calcium absorption from ES-$CaCO_3$ compared to synthetic $CaCO_3$. The few available human pharmacokinetic studies also suggest equivalent calcium bioavailability. However, large-scale randomized controlled clinical trials specifically comparing ES-$CaCO_3$ supplementation with pharmaceutical-grade $CaCO_3$ in relevant patient populations (postmenopausal women, CKD patients, children with rickets) are lacking. Such trials would be required before regulatory agencies could approve specific therapeutic claims for ES-$CaCO_3$ as a distinct entity.

8.3 Formulation Performance Across Dosage Forms

Each of the five formulation categories reviewed demonstrates a distinct set of advantages and challenges when incorporating ES-$CaCO_3$. Conventional tablets and capsules offer the most straightforward path to pharmaceutical use because the existing regulatory framework and manufacturing infrastructure are well-established. The primary challenge in tablet formulations is particle size control: excessively coarse ES-$CaCO_3$ leads to poor compressibility and tablet friability, while excessively fine particles may cause dusting and flow problems. Optimizing the particle size distribution through controlled milling and classification is essential.

Oral suspensions offer the advantage of dose flexibility and suitability for vulnerable patient populations. The major formulation challenge is physical stability: ES-$CaCO_3$ suspensions tend to sediment rapidly without adequate suspending agents and viscosity modifiers. Optimizing the rheological properties of the continuous phase, combined with particle size reduction, is critical for achieving acceptable product quality and shelf life.

Medicated chewing gum represents the most innovative conventional-to-novel transition for ES-$CaCO_3$, capitalizing on the growing consumer preference for functional confections and drug delivery through non-traditional platforms. The primary challenge is achieving uniform distribution of ES-$CaCO_3$ within the gum matrix without compromising texture or flavor. ES-$CaCO_3$ particles must be sufficiently fine (< 100 μm) to avoid grittiness during chewing. Additionally, the alkaline nature of ES-$CaCO_3$ may interact with acidic flavor compounds, necessitating careful flavor selection and sequestering strategies.

Floating gastroretentive tablets leveraging ES-$CaCO_3$ as both an active ingredient and a CO_2 gas generator represent a highly innovative and scientifically elegant formulation approach. The dual functionality eliminates the need for separate gas-generating agents (such as sodium bicarbonate) that might interact with the active or alter the pH of the immediate release environment. However, this approach introduces additional formulation complexity: the stoichiometry of CO_2 generation must be precisely calibrated to ensure adequate buoyancy without premature drug release. Moreover, the performance of floating tablets is inherently dependent on the fed/fasted state of the stomach, which varies between patients and affects gastric acid concentration available to react with ES-$CaCO_3$.

8.4 Environmental and Economic Impact

The environmental and economic arguments for ES-$CaCO_3$ use in pharmaceuticals are compelling. Global eggshell waste represents an enormous underutilized resource. The valorization of this biowaste stream into pharmaceutical-grade $CaCO_3$ not only reduces landfill burden but also offsets the need for limestone mining, which carries significant ecological impacts including habitat disruption, CO_2 emissions from calcination, and acid mine drainage. Life cycle analyses comparing ES-$CaCO_3$ with mined $CaCO_3$ have estimated a 20–40% reduction in carbon footprint for ES-$CaCO_3$, depending on the geographic context and processing method.

From an economic standpoint, eggshell collection and processing costs are significantly lower than the costs of mining, crushing, and purifying limestone to pharmaceutical purity standards. For developing countries with large poultry industries (including India, China, Brazil), the establishment of regional ES-$CaCO_3$ processing facilities could create economic value from waste while supplying affordable pharmaceutical-grade excipients to local manufacturers.

9. FUTURE SCOPE

Despite the substantial body of research reviewed herein, numerous opportunities for further investigation and application development remain.

- Large-Scale Clinical Trials: Well-designed, randomized, double-blind, controlled clinical trials are urgently needed to establish the bioequivalence and therapeutic non-inferiority of ES-$CaCO_3$ relative to pharmaceutical-grade $CaCO_3$ in diverse patient populations, including pediatric patients, postmenopausal women, and patients with chronic kidney disease. Such trials would form the evidentiary basis for regulatory approval of specific therapeutic indications.
- Nanoparticle Development: The synthesis of ES-$CaCO_3$ nanoparticles with controlled size (50–200 nm), surface modification, and encapsulation efficiency opens exciting avenues in targeted drug delivery, particularly for cancer therapy and intracellular delivery of nucleic acid therapeutics. The pH-responsive dissolution of $CaCO_3$ nanoparticles in the tumor microenvironment and endolysosomes makes them ideal “smart” delivery vehicles. Future work should focus on scalable synthesis methods, surface functionalization strategies (PEGylation, ligand conjugation), and in vivo evaluation in relevant tumor models.
- 3D Printing and Personalized Medicine: The emerging field of pharmaceutical 3D printing (additive manufacturing) presents opportunities for incorporating ES-$CaCO_3$ into printed dosage forms with customizable geometry, dose, and release profiles. $CaCO_3$'s compatibility with hot-melt extrusion (HME) and powder bed fusion (PBF) printing technologies should be systematically evaluated. Personalized calcium supplementation tablets with dose titrated to individual patient requirements could be manufactured on-demand at the point of care.
- Composite Biomaterials for Bone and Dental Tissue Engineering: The development of ES-$CaCO_3$/hydroxyapatite/biopolymer composite scaffolds for bone and dental tissue engineering represents a high-impact future direction. These scaffolds combine the osteoconductivity of $CaCO_3$, the biocompatibility of hydroxyapatite, and the architectural flexibility of polymer matrices (e.g., PLGA, collagen, chitosan). In vitro and in vivo evaluation of osteoblast and osteoclast responses to these composites, along with mechanical testing and degradation studies, are research priorities.
- Pharmacopoeial Standardization: The development of dedicated pharmacopoeial monographs and quality standards for ES-$CaCO_3$ as a pharmaceutical ingredient is a critical regulatory priority. This would include specification setting for eggshell source species, extraction process parameters, permissible biological contaminants (prions, pathogens), and acceptance criteria for characterization tests. Collaboration between regulatory agencies (FDA, EMA, CDSCO), pharmacopoeial bodies, and industry is needed to advance this objective.
- Microbiome and Prebiotic Interactions: Emerging evidence suggests that $CaCO_3$ may modulate the gut microbiome through its pH-altering effects, which could have downstream implications for metabolic health, immune function, and drug absorption. The specific microbiome-modulating effects of ES-$CaCO_3$ (with its unique trace mineral and organic matter profile) compared to synthetic $CaCO_3$ deserve systematic investigation in both animal models and clinical studies.
- Industrial Scalability and Standardization of Extraction: While laboratory-scale extraction of ES-$CaCO_3$ is well-characterized, industrial-scale processing must address challenges including variability in eggshell composition (influenced by hen breed, age, diet, and season), batch-to-batch consistency, energy-efficient processing, and waste effluent management. Development of continuous manufacturing processes and robust quality-by-design (QbD) frameworks for ES-$CaCO_3$ production would facilitate its commercialization at scale.

10. CONCLUSION

This review has comprehensively examined eggshell-derived calcium carbonate as a pharmaceutical ingredient, detailing its extraction, characterization, pharmacological activities, and diverse formulation applications. The evidence presented demonstrates that ES-$CaCO_3$ is not merely a curiosity or a sustainable alternative to mined or synthetic $CaCO_3$; it is a scientifically validated, pharmacologically effective, and

environmentally responsible pharmaceutical raw material. Its chemical equivalence to pharmacopoeial $CaCO_3$, combined with its natural trace mineral composition and low heavy metal burden, makes it an attractive candidate for adoption across the full spectrum of $CaCO_3$-based pharmaceutical products.

The five formulation platforms reviewed, namely conventional tablets, hard gelatin capsules, oral suspensions, medicated chewing gum, and floating gastroretentive tablets, each leverage the unique properties of ES-$CaCO_3$ in different ways and offer complementary approaches to calcium delivery and antacid therapy. The novel delivery systems, in particular, represent exciting frontiers where the dual functionality of ES-$CaCO_3$ as an active ingredient and a formulation component (gas generator, pH modifier, matrix filler) can be creatively exploited.

The path to widespread pharmaceutical adoption of ES-$CaCO_3$ requires concerted efforts in clinical validation, pharmacopoeial standardization, and industrial process development. Given the global urgency of sustainable manufacturing and circular economy principles, investment in this area is not only scientifically justified but also environmentally and economically imperative. Eggshell-derived calcium carbonate has the potential to transform an agricultural waste stream into a high-value pharmaceutical ingredient, contributing to healthier patients and a healthier planet.

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