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NOVEL APPLICATIONS OF PRECIPITATED CALCIUM CARBONATE IN FOOD, PHARMACEUTICAL, AND COSMETIC INDUSTRY

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Abstract
Globally, different types of industries have been using precipitated calcium carbonate (PCC) from decades. Yet some recent studies have shown that there are some novel uses/applications of PCC in food, pharmaceutical, and cosmetic industries beyond traditional applications. It can be used in old materials which have already been prepared with variations or in the development of new materials. This paper critically summarizes the basic production methods, uses/applications, recent development and ongoing activities, specifications, and regulations for the use of food-grade PCC materials. The review would allow academics, researchers and industrialists to learn about the material and innovations that have occurred in the last few years. Moreover, this paper provides an update of the most recent and relevant findings about the selected material application in different types of industries. The review paper also focuses the future research needs and provides new insights and directions for the application of PCC in related industries.

Keywords: Precipitated calcium carbonate; Food grade calcium carbonate; Ground calcium carbonate; food, pharmaceutical industries

Introduction

In different types of industries, calcium carbonate uses for the preparation of various products. There are two types of calcium carbonate, i) ground calcium carbonate (GCC) and ii) precipitated calcium carbonate (PCC). GCC normally has a size of 10 micrometers, while PCC is around one-tenth of the nanometer (Roskill, 2005). It is used, directly or indirectly, in various industries. The direct uses of calcium are occurred in industries such as cement, ceramics, sugar and building materials, while indirect use requires early processing of calcium carbonate in the food, pharmaceutical and cosmetic industries in the form of PCC. In 2011, world consumption of precipitated material (PCC) per year was reported about 14 mega-tons (Roskill, 2012).

However, PCC is safe for food, pharmaceutical and cosmetic products until it meets the requirements for purity as set out in Table 1. (Commission Regulation, 2012; USP United States Pharmacopeia

Convention, 2015; EP (European Pharmacopeia, 2015), JP (Japanese Pharmacopeia, 2006; JECFA,2006). In food, it is used as a regulator of acidity, anti-caking agent and firming agent. It also uses as treatment agent in flour, as a stabilizer (Codex Alimentarius, 2019), and as a coloring agent to make food look pleasant (Wiley and Yen Nee, 2020). It also uses as an excipient and antacid in pharmaceutical (Medicines. M.H.R.A., 2015) and cosmetics products (Regulation 2019/681/EU, 2019). For food application, the average particle size d50% should be 5 µm, with an upper range d98% of 65 µm (CCA-Europe, 2011). The purity of calcium carbonate along with heavy metals and others parameters required for use in food and pharmaceutical industries is mentioned in the table 1 below.

Table 1: Different specifications of calcium carbonate for food, pharmaceuticals, and cosmetics industries

Parameter	**Regulation Reference**				
	Commission Regulation (231/2012/EU)	**Eur. Ph. (2015)**	**USP (2015)**	**JP (2006)**	**JECFA (2006)**
Purity of $CaCO_3$	≥ 98.00%	98.50–100.50%	98.50–100.50%	≥ 98.50%	≥ 98.00%
Loss on drying (200 °C, 4 hours)	≤ 02.00%	≤ 02.00%	≤ 2.0%	≤ 1.0% 180 °C, 4 hours	≤ 2.0%
Insoluble matter/substances	≤ 00.20%	≤ 00.20%	≤ 00.20%	≤ 00.20%	≤ 00.20%
Free alkali	-	≤ 00.05%	≤ 00.05%	≤ 00.05%	≤ 00.05%
Chloride as Cl	n.s	330 ppm	n.s	n.s	n.s
Magnesium and Alkali salts	≤ 01.00%	≤ 01.50%	≤ 01.05%	≤ 01.00%	≤ 01.00%
Fluoride as F	≤50.00 mg/kg	≤50.00 mg/kg	n.s	n.s	n.s
Antimony as Sb Copper as Cu Chromium as Cr Zinc as Zn	≤ 100.00 mg/kg, singly or in combination	≤ 20.00 mg/kg in combination	≤ 20.00 mg/kg in combination	≤ 20.00 mg/kg in combination	n.s
Barium as Ba					≤ 00.03%
Arsenic as As	≤ 03.00 mg/kg	≤ 04.00 mg/kg	≤ 03.00 mg/kg	≤ 05.00 mg/kg	≤ 03.00 mg/kg
Lead as Pb	≤ 03.00 mg/kg	n.s	≤ 03.00 mg/kg	n.s	≤ 03.00 mg/kg
Cadmium as Cd	≤ 01.00 mg/kg	n.s	n.s	n.s	n.s
Iron as Fe	n.s	00.10%	≤ 200.00 mg/kg	n.s	n.s
Mercury as Hg	n.s	n.s	≤ 00.50 mg/kg	n.s	n.s

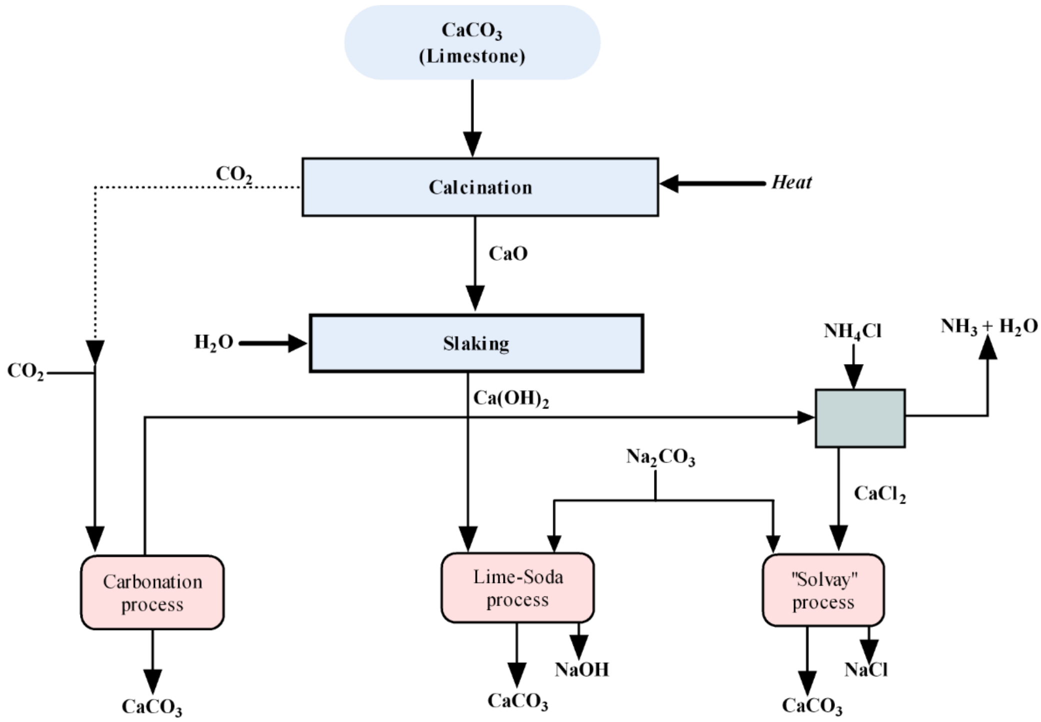
n.s (not specified)

Commission Regulation 231/2012/EU *(2012), USP (United States Pharmacopeia Convention, 2015), Eur. Ph. (European Pharmacopeia, 2015), JP (Japanese Pharmacopeia, 2006), JECFA,2006 (Joint FAO/WHO expert committee on food additives, Rome).*

Calcium Carbonate is registered under the REACH Regulations (Council Regulation No 1907/2006/EC, 2006) and can be used as an additive in various food items and drugs (U. S. Food and Drug Administration, 2017).

PCC has a uniform shape and is more efficient in different industries as compared to other types of c alcium carbonate because of its properties (Seo et al., 2005). It is easily prepared, biodegradable, bio compatible and easily available raw material in enormous quantities and also very cheap (Mantilaka et al., 2014; Long et al., 2013; Guo et al., 2013).

The method of PCC production has a role in its purity, prepared by three common processes (Lime soda, Carbonation, and Solvay or calcium chloride process).



Eloneva, (2010); Hagemeyer, 1983)

Fig. 1: Typical methods used for preparation of PCC

PCC produced from the Solvay or calcium chloride material is the oldest, simplest, low cost and financially viable method as shown in the equation (1).

$$Na_2CO_3 + CaCl_2 \leftrightarrows CaCO_3 + 2NaCl \quad \text{..................(1)}$$

The PCC produced from the above-mentioned method has fewer impurities than other methods like carbonation and soda-lime processes because calcium is used indirectly as $CaCl_2$ (Table 2). As the limestone is first treated with acid, so the impurities present in the limestone are removed earlier in the process (Fig. 1) (Hagemeyer, 1983).

Table 2: Typical chemical composition of PCC prepared by different production methods

Parameters	**Production processes**		
	Carbonation	**Lime-soda**	**Solvay**
$CaCO_3$ (%)	98.36	98.43	98.62
$CaSO_4$ (%)	00.08	00.78	00.63
$MgCO_3$ (%)	00.70	00.37	00.21
Al_2O_3 (%)	00.09	00.07	00.01
Fe_2O_3 (%)	00.07	00.06	00.01
SiO_2 (%)	00.10	00.04	00.02
Moisture (%)	00.60	00.25	00.30
pH	09.40	10.30	08.50

Source: (Hagemeyer, 1983)

People of the world are depending on PCC more than any other time of history. Its uses are extended from the manufacture of the product to the customer. There is surfeit literature on the multiple applications of PCC worldwide in different industries, but no review study on the novel food-grade PCC applications in various industries has been conducted previously. In this review, the areas selected where the research work is done recently and critically discussed. This review will provide some novel applications of PCC especially in food, pharmaceuticals, and cosmetics industries and discuss their specifications according to the industries. It will also focus on the updated knowledge and provide new directions for future research to meet the needs of industries.

1 Pharmaceutical and application of PCC

1.1 As an Antiacid

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders (Dent et al., 2005). To cater to the GERD problem, medical practitioners encourage patients to use over-the-counter drugs such as anti-acids besides management of the disease (Roark et al., 2019). Anti-reflux formulations are one of the famous pharmaceutical industrial products made from PCC (Sontag, 1990). It is as an alkalizing agent with liquid sodium alginate suspension. Recent investigations showed that it gives faster relief from acid reflux and neutralize stomach acid (Table 3). Sodium alginate 5% and PCC 1.6% showed positive effects on the acid-neutralizing capacity value of 20.83 mEq (Torne et al., 2020). In recent developments, its potential in raft forming formulation studied to prepare sustained-release aqueous suspensions for use as an antacid. Raft forming suspension is liquid when administered but becomes gels when coming in contact with the gastric contents. This gel floats on the gastric contents and prevents them from getting reflux into the esophagus. Sodium alginate and PCC were used as a raft-forming vehicle to overcome physiological problems like gastric retention variation and emptying time (Bani-Jaber et al., 2020). If some peoples may have difficulty in swallowing of tablets so chewable tablets containing PCC and nizatidine (as histamine H2 antagonist) is developed, which is broken down between the teeth before ingestion. This raft forming formulation has rapid relief in acid burning symptoms besides delivering a drug into the systemic circulation (Darwish et al., 2019).

PCC also proved beneficial in pregnancy and lactation as nearly two-thirds of the women experience heartburn during pregnancy. Mild symptoms can be treated with the lifestyle changes, but if the problem exceeds then pharmaceutical/therapeutic agents may be considered. PCC as an ant-acid is a first-line therapeutic agent, the formulation developed from PCC is also safe during lactation lactation (Thelin and Richter, 2020).

1.2 Supplements

Calcium is the essential nutrient of the human body needed for various functions. The human body gets most of the nutrient from the absorption of the calcium in food we eat, but for low absorption and phytates and oxalates in the body, the absorption reduces. Supplement is, therefore used to overcome the reduction of body nutrients (Indu et al., 2019).

Food grade PCC used in several supplements and calcium-enriched formulas. Calcium-enriched drain is much supportive within the avoidance of bone break and osteoporosis and ovarian hormone insufficiency for menopausal ladies (Erfanian et al., 2017). The maximum calcium dose in typical conditions ought to be 500 mg but requires 600-800 mg/day for pregnant and lactating mothers. It requires a longer term of utilize for osteopenia and osteoporosis patients. For most extreme assimilation, we ought to take calcium supplements with a feast (Trailokya et al., 2017).

Almost 3.5 billion peoples in the world are calcium deficient (Kumssa et al., 2015). When a low dose of calcium taken, it results in the mobilization of calcium from bones, so decreasing bone mineral density causing osteopenia and osteoporosis (Riggs and Melton, 1995). It will further cause continuous pain, frequent fractures, and loss of movement/mobility (Reginster and Burlet, 2006).

A dose above 1200-1500 mg/day of calcium not recommended and excessive intake may increase the risk of cardiovascular disease, stroke (Reid and Bolland, 2012; Chae et al., 2019; Bolland et al., 2011; Moyer, 2013) and developing kidney stone (Ferraro et al., 2020 and Prentice et al., 2013)

Osteoporosis is treatable before fracture of bone occurs; it is also treatable even after the first fracture occurs. National osteoporosis foundation (NOF) in collaboration with a multispecialty council of medical experts of bone health has recommended varying doses of calcium for postmenopausal women and men age 50 and older (Cosman et al., 2014). It is recommended for men to use 1000 mg of calcium per day up to 50-70 age, while women above 51 and men above 71 should consume 1200 mg per day (Cosman et al., 2014 and Ross et al., 2011). Hypoparathyroid patients develop hypocalcemia (lower calcium level in blood) after surgery (thyroidectomy) a preventive calcium supplementation is required for an effective cure of the problem (Nicholson et al., 2019; Akkan et al., 2020). Some studies done on the efficacy of the nano form of PCC as dietary supplements and checked the effect of particle size on the cytotoxicity, uptake by cell, transport by the intestine, and oral absorption. The findings of these studies showed increased uptake behavior and rapid absorption of calcium carbonate, but the rate of absorption was slower. This means that the size of calcium carbonate not changed the total absorption efficiency and proved that conventional PCC has more oral efficacy than nanoscale calcium carbonate (Kim et al., 2015). The eggshell is a cheap source of calcium carbonate and used as a value-added industrial product. To fulfill the dietary requirement of the people, fortification of food can be done by preparing a calcium supplement with PCC. This formulation will be beneficial to cater to the nutritional requirements and the minimization of environmental pollution (Waheed et al., 2019).

1.3 PCC uses in other medicines

Eco-friendly medication chewing gum with 80 mg of calcium carbonate produced for motion sickness. Wheat grain used as a natural gum base for its availability, biocompatibility, and biodegradability. Prolamin extracted from wheat for its elasticity, chewing capacity, antifungal activity, and high-water retention capacity. The importance of this eco-friendly medicine is the use of rapid drug release, 90% drug release achieved within 16 minutes of chewing (Shete et al., 2015).

Gastric cancer is the major cause of death in cancer patients. In this disease, a patient develops a tumor called malignant neoplasms (Ferlay et al., 2015; Torre et al., 2015). The suspension using calcium carbonate showed a marvelous impact on patients having malignant neoplasm. The study showed that the calcium carbonate-based suspension affects the activation mechanism of epithelial-mesenchymal transition during carcinogenesis or inflammation (Senchukova et al., 2019).

PCC has also biomedical applications in the pharmaceutical industry, often used as bulking or coating agent as a diluent, for a hybrid carrier of genes, proteins and drugs and also as a drug delivery system (Fig. 2) because of its degradability and bio biocompatibility (Avaro et al., 2019; Li et al., 2020; Saveleva et al., 2018). Recently in research PCC and silver particles composite used in the healing of burns wound (Matei et al., 2019). In the pharmaceutical industry, the development of the PCC hybrid particles can also enhance its use by rapid precipitation methods that are pH-sensitive and biocompatible. Upon exposure to low pH, these particles generate CO_2 bubbles making them contrast agents and used for the detection of tumor cells by enhancing the ultrasound image. Hence a wonderful addition for drug delivery and identification of tumor cells (Vidallon et al., 2020).

Nanoparticles are material having nano size properties and are superior to ordinary calcium carbonate particles for drug delivery because of its bioavailability and biocompatibility as they are sensitive to pH. In cancer treatment anticancer drugs cannot distinguish between cancer and healthy cell (Bisht and Maitra, 2009; Duesberg et al., 2007; Zhu et al., 2014), therefore nano calcium carbonate used for efficient drug delivery system (Allen and Cullis, 2004; Zhao et al., 2012).

CaCO3 nanoparticles used as a carrier, chitosan as assembly materials, while folic acid as target molecules. The results of the study showed that the mesopores form of nano calcium carbonate has a substantial clinical application in cancer therapy (Xing et al., 2020).

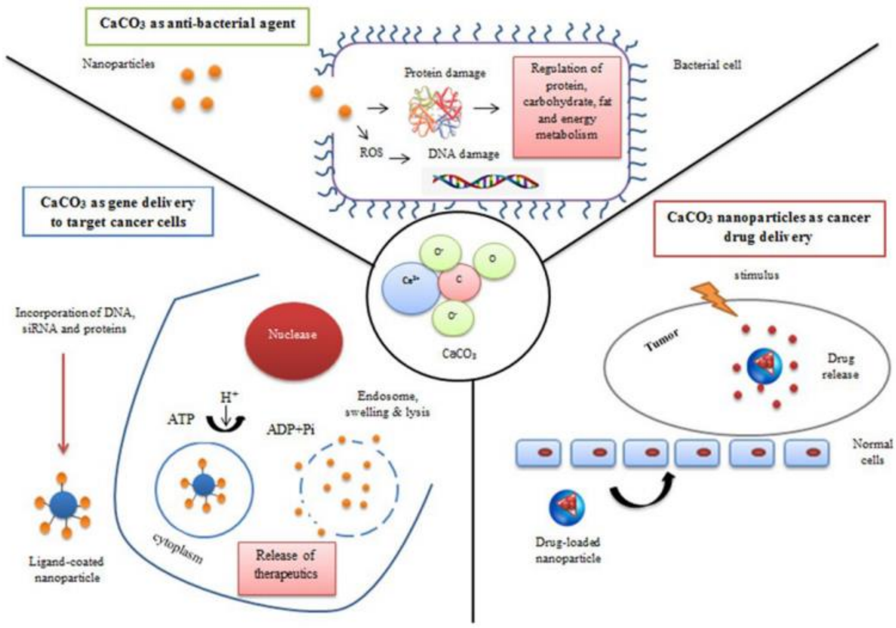


Figure 2: The uses of PCC nanoparticles as anti-microbial, drug and gene delivery agent in therapeutic purposes (Basria et al., 2018)

2 Food and PCC application

The addition of PCC or fortification of calcium as a source shows better organoleptic acceptability in rice extrudates and noodles to overcome the fractures due to osteoporosis and further studies can be carried out on the fortification of cereals, beverages and bakery products.

In bakery items, we can add PCC in preparing muffins at an 8 g/500g flour basis. Mineral analysis results showed an increase in mineral concentration and better organoleptic acceptability and increase properties such as color, flavor, texture, and taste (Afzal et al., 2020). Recent studies are also of the view to use nanosized minerals in the food industry for fortification, nutritional supplements, and in other industrial applications. (Peters et al., 2016; d'Amora et al., 2020). PCC nanoparticles used as an additive in the chewing gum along with TiO_2 nanoparticle (Dudefoi et al., 2018). Using nanoparticles is increasing in the food industry and in a variety of food products as food fortification and supplements (Table 3), but most of the food industries are reluctant to use it. The reason may be its cost, safety, and labeling of the product. It has a high surface area and therefore they are readily bioavailable (Knijnenburg et al., 2019). but it requires further research for the routine use/applications of minerals as nanomaterials especially for fortification (Gallocchio et al., 2015). Information on the permission/approval of calcium carbonate used in food as an additive or added nutrient source has explained in Table 4.

3 Cosmetics industries and PCC

Use of calcium carbonate in cosmetic beauty products is ancient. Recent studies showed that the maximum use of PCC is in the production of toothpaste. Toothpaste is a hygiene product, and it requires to be used daily. Several research studies showed that brushing with toothpaste does not remove the plaque (Valkenburg et al., 2016; Paraskevas et al., 2007 and Jayakumar et al., 2010), while instead brushing with a toothpaste having granulated PCC improves the cleaning efficacy because it reaches the spaces with bristles (Nishigawa et al., 1992; Yamagishi et al., 1990). Granulated calcium carbonate as a cleaning agent with a particle size of 250 µm gives the best result (Eda et al., 2019; Endoh et al., 2019).

PCC is very cheap than other abrasive dentifrice materials like di-calcium phosphate and silica (Huwald, 2001). There are several studies nowadays on the use of nano calcium carbonate in toothpaste formulations. As the abrasives present in the toothpaste affect the surface roughness of the tooth and the restorative material (Rahardjo et al., 2015) Rough surface of the tooth and restorative material are places for the accumulation of plaque (Mallya et al., 2013 and Rahardjo et al., 2015).

Brushing with nano calcium, carbonate abrasive decreases the roughness of the tooth and restorative material (Anisja., 2017).

Recent researches studies proved the use of PCC nanoparticle application in various industries (Fig. 3) and have also got attention nowadays not only as filler in nano-composites but a catalyst in cosmetics and as a carrier for drug delivery (Wei et al., 2020; Elbaz et al., 2019; Stark et al., 2015 and Vance et al., 2015). Nanoparticles have a large surface area because of which they interact with one another and form micronized agglomerates that reduces surface energy (Hosokawa et al., 2008).

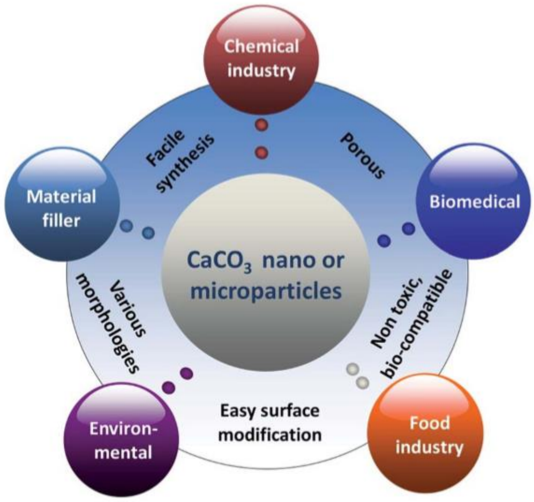


Fig. 3 Applications and properties of calcium carbonate nanoparticles (Boyjoo et al., 2014)

Table 3: Summary of the application and uses of Food grade PCC in different formulations in different industries i.e. food, pharmaceutical, and cosmetics.

Group	Category	Principal function	Benefits achieved/Effects	References
Pharmaceutical and medicines	Antacid for gastroesophageal reflux	Alkalizing agents	improve the acid neutralization capacity	Torne et al. (2020) Katsube et al. (2019) Darwish et al. (2019)
	Chewing tablets for Hyperphosphatemia end-stage kidney disease	Binding agent	physiological changes in the GI tract and alter the gut microbiota	Barreto et al. (2019)
	Chewing Gum for motion sickness	Texturizer	rapid drug release and antifungal activity	Shete et al. (2015)
	Suspension for Gastric tumor or malignant neoplasms.	Cytotoxic effect	Reduced inflammation and activation of epithelial–mesenchymal transition	Senchukova et al. (2019)
	Powder for medical and pharmaceutical applications.	as a diluent, bulking or coating agent	a hybrid carrier for drugs, proteins, and genes	Avaro et al. (2019)
	Milk for Increase bioavailability and absorption of calcium	Dietary supplement	prevent bone loss and fracture induced by osteoporosis	Erfanian et al. (2017)
	Increase absorption	Dietary supplement	ensure a healthy skeleton	Trailokya et al. (2017)
	Hypocalcemia (lower calcium level in blood)	Supplement	Prevention of hypocalcemia	Nicholson et al. (2019) Akkan et al. (2020)

Food	Bone weakness	Dietary supplement	prevention, diagnosis, and treatment of osteoporosis in postmenopausal women and men age 50 and older	Cosman et al. (2014)
	Calcium delivery systems based on natural products such as proteins and polysaccharides for calcium bioavailability	Dietary supplement	enhance bone synthesis to prevent calcium deficiency and conducive to gut health	Zhu et al. (2020)
	Rice and rice noodles Nutrient deficiency	Fortifying agent	lowered bulk density, improved texture, lower oil uptake and increase organoleptic acceptability of rice and noodles used for prevention of osteoporosis	Janve et al. (2018)
	Muffin for nutrient deficiency	Fortifying agent	enhanced texture and increase organoleptic acceptability	Afzal et al. (2020)
Cosmetics	Toothpaste for plaque, debris and surface stains	Cleaning agent	plague removal, gingival health and positive effect on periodontal tissue	Endoh et al. (2020)
	Toothpaste for Plaque and surface stain	Abrasive agents	alter tooth and restorative material surfaces	Anisja et al. (2017)

Table 4: Information on the permission/approval of calcium carbonate as a food additive or added nutrient source.

Food group	function	Reported range	Allowed by
Sweeteners for use in foodstuffs	Additive	-	Council Directive 2006/52/EC (2006) Codex Alimentarius. (2019)
Soft drinks (as an additive)	Coloring Agent	500mg/kg (max)	Council Directive 94/36/EC (1994) Wiley et, al. (2020)
nutritional purposes in foods	nutrient	-	Commission Directive 2001/15/EC (2001)
food supplements as an additive	nutrient	1000-1500 mg Ca	Council Directive 2002/46/EC (2002)
food supplements	nutrient	800 mg calcium/day (Max)	EFSA, (2011)
Confectionery	release agent	400 mg/kg typical use level	EFSA, (2011)
Rusk	Additive	5000-12000 mg/kg	EFSA, (2011)
Chocolate (additive)	Bulking agent	Typical use level 50000 mg/kg	EFSA, (2011)
Sausages (Meat curing surface treatment)	additive	7g/kg maximum use level	EFSA, (2011)
Vitamin and Mineral		-	Council Regulation 108/2008/EC (2008)
Cosmetics	colorant	≥ 98% $CaCO_3$ purity	Commission Regulation 2019/681/EU (2019)
Pharmacology and Pharmaceutical	As an excipient and as an Antacid	-	USP, (2015) Ph. Eur. (2009) (Medicines. M.H.R.A., 2015)
Daily Dietary Calcium intake	nutrient	400-1200 mg/day depending on age and gender	EFSA, (2011); US food and Drug Administration, (2006) and Hanzlik, et, al 2005

Conclusions

Recent and novel precipitated calcium carbonate use and applications in various products have transformed from micro to nanomaterials. A Recent review study shows that the use expanded as a biomedical application in the pharmaceutical industry as a hybrid carrier of genes and proteins, as well as for drug delivery and as a raft forming formulation. In the food industry, as a food supplement and for food fortification. Because of bioavailability and biocompatibility, the use of nano-size material is expected to increase in the future but its routine application requires a complete understanding of the toxicity and safety. Nanotechnology should be carefully adopted until complete safety data is available for customer protection. So, this review suggests that the use of PCC in the new materials is increasing but there is still a gap that exists on the safety of PCC nano-material. Interaction of food with the nano-materials and their effect on the body after ingestion should be studied before applicability for various uses.

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