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Historical perspective

Silica-based systems for oral delivery of drugs, macromolecules and cells

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ABSTRACT

According to the US Food and Drug Administration and the European Food Safety Authority, amorphous forms of silica and silicates are generally recognized to be safe as oral delivery ingredients in amounts up to 1500 mg per day. Silica is used in the formulation of solid dosage forms, e.g. tablets, as glidant or lubricant.

The synthesis of silica-based materials depends on the payload nature, drug, macromolecule or cell, and on the target release (active or passive). In the literature, most of the examples deal with the encapsulation of drugs in mesoporous silica nanoparticles. Still to date limited reports concerning the delivery of encapsulated macromolecules and cells have been reported in the field of oral delivery, despite the multiple promising examples demonstrating the compatibility of the sol-gel route with biological entities, likewise the interest of silica as an oral carrier. Silica diatoms appear as an elegant, cost-effective and promising alternative to synthetic sol-gel-based materials.

This review reports the latest advances silica-based systems and discusses the potential benefits and drawbacks of using silica for oral delivery of drugs, macromolecules or cells.

1. Introduction

Silicon dioxide, SiO_2, generally called silica, is abundantly distributed in earth's crust as silicate minerals but also in plants, cereals and fruits. Also, some living organisms such as siliceous sponges have an amorphous skeleton generated by an enzyme, the silicatein [1]. Interestingly, human body also contains silicon in its skeleton, blood vessels, heart, muscles, skin, hair, ligaments, cartilage and in nails where the highest concentration is found [2].

Crystalline or amorphous, silica can be obtained from natural sources or synthetically through wet or thermal processes. Among those synthetic routes, sol-gel is by far the most used and versatile process especially to obtain mesoporous materials, with high surface areas and pore volumes [3]. The pore channels can be highly ordered (in hexagonal or cubic arrangements) and with sizes tunable in the range of 2 to 50 nm. Moreover, the presence of silanol groups (Si-OH) on the inner and outer surface of the material facilitates its chemical functionalization by specific groups related to the desired application. These structural and chemical properties make mesoporous materials suitable for adsorption of pollutants, as polymer fillers and catalysis, where high adsorption capacities and chemical tuning are strongly appreciated [4].

Beyond those applications, nanomedecine is also of high interest. Drug delivery and bio-imaging are topics in which the use of mesoporous silica nanoparticles (MSN) is becoming popular especially because of its biocompatibility and capacity to uptake poorly soluble drugs. Scientific literature is describing more and more sophisticated targeted silica carriers that are stimuli-responsive multifunctional platforms to allow both diagnostic and therapy, known as the theranostic approach.

Nowadays, great efforts are made to develop smart drug delivery systems (DDS) for different administration routes, including the oral one. Yet this route is the most comfortable for the patient and the most efficient, although the gastro-intestinal barrier remains challenging. Before being approved as nontoxic and biodegradable, silica was already used as excipients in medicine and food additives (E551). In fact according to the US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), amorphous forms of silica and silicates are generally recognized to be safe as oral delivery ingredients in amounts up to 1500 mg per day [5].

In this context, this review aims to give an extended overview on the

Abbreviations: BCS, biopharmaceutical classification system; DDS, drug delivery system; DSMs, diatom silica microparticles; DRF, dose range finding; EFSA, European Food Safety Authority; FDA, US Food and Drug Administration; Ery, erythromycin; GIT, gastro-intestinal tract; Ibu, Ibuprofen; MCM, Mobil Composition of Matter series; MSN, mesoporous silica nanoparticles; NOAEL, no observed adverse effects level; ODDS, oral drug delivery system; NP, nanoparticles; SBA, Santa Barbara type; SBF, simulated body fluid; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; SiNP, silica nanoparticle; SSPI, succinylated soy protein isolate; TEOS, tetraethylortosilicate; TMOS, tetramethylortosilicate

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latest advances on the use of silica in oral delivery systems including drugs, proteins, *e.g.* enzymes, hormones, or even cells, *e.g.* probiotic bacteria, systems used for the elaboration of functional food or oral pharmaceutical dosage forms.

In the first part of this review, the synthesis of various kinds of amorphous silica materials by the sol-gel process is summarized. In the second part, silica-based oral drug delivery systems (ODDS) are presented, while the third part deals with their benefits and health risks. The final part is a summary and an outlook on silica carriers for oral delivery.

2. Prerequisite for oral delivery systems

Noninvasive, accessible, simple and economical, the oral administration remains at the top of the prescribed and over-the-counter medications over the world. Therefore, it is not surprising that, whenever possible, clinicians prefer to prescribe oral dosage forms instead of parenteral ones which are not only invasive, but require medical interventions and occasionally hospitalization. Several intravenous-to-oral route conversion programs were implemented in hospitals with the aim to reduce the infection risk inherent to intravenous administration, to reduce medication costs and also to improve patients' compliance [6,7,8,9,10,11].

Great research efforts have been and are still being dedicated to the development of oral dosage forms that might substitute/limit the use of parenteral dosage forms. Nevertheless, the design of drug products for the oral route remains challenging. Indeed, the drug passage through the gastro-intestinal tract (GIT) is harsh on drugs, which will encounter several barriers before reaching the systemic circulation. Several factors are involved: i) the gastric pH that is as low as 1 in fast conditions; ii) the presence of hydrolytic enzymes in the gastric and intestinal juices; iii) the intestinal drug efflux by *P*-glycoprotein pumps localized in enterocytes' apical membranes; and iv) the premature drug catabolism by the hepatic and/or intestinal cytochrome P450 [12].

The success of this passage partially on the drug's own physico-chemical properties such as water solubility, molecular weight, partition coefficient [13] and also on those of the pharmaceutical DDS. The design of ODDS could be adjusted to ensure other functions beyond the protection of the payload from its premature degradation. In this respect we can mention: i) the **gastro-retention** sought for different purposes, *e.g.* to achieve a local action in the stomach, to enhance the absorption of drugs within a narrow window or even to enhance the stability of unstable drugs in the intestinal juice [14]; ii) the **gastro-resistance** of drugs that are subjected to degradation in the severe gastric environment or conversely, to protect the gastric mucus against drugs' irritant effects; iii) the **sustained release** aiming a reduction in dosing frequency and therefore improving the patients' compliance; iv) the **triggered release** to a specific site, *e.g.* targeting a high drug amount directly on specific cells in the colon; v) the **mucoadhesion** on the intestinal epithelium allowing the increase of the intestinal residence time, and thus a longer time for drug absorption; vi) an **enhancement of the dissolution rate** of drugs of class II and IV (according to the biopharmaceutical classification system).

The above-mentioned functions of ODDS could be reached by using the appropriate formulation from the wide range of ingredients nowadays available. For instance, polysaccharides, *e.g.* chitosan, cellulose, starch and their derivatives, alginates, pectin, and acacia gum, proteins, *e.g.* albumin, gelatin and gliadin, polymethacrylates bearing quaternary ammonium groups (Eudragit ® RS/Eudragit ® RL) are all mucoadhesive polymers allowing for a close contact of payloads with the intestinal epithelium for an extended time period. Moreover, in the formulation of hydrophilic matrix tablets and micro- and nanoparticulate DDS, these polymers form a swellable network enabling a sustained diffusion of drugs. Furthermore, theses polymers are able to promote the paracellular transport through the intestinal epithelium by producing a transient opening of the tight junctions between the enterocytes [15,16].

The gastro-resistance becomes possible thanks to pH-sensitive polymers such as, cellulose acetato-phthalate and Eudragit ® L or Eudragit ® S. The unique feature of these polymers is the presence of carboxylic groups (–COOH). In the acidic gastric juice where the pH is below the pKa of carboxylic acid groups (≈ 4), the protonated form (water insoluble) is predominant, what constitutes a physical barrier against drug release. In the intestinal juice, the pH is higher than 4 what leads to polymer deprotonation, dissolution and thus allowing drug release.

The enhancement of the dissolution of poorly soluble drugs is carried out using a variety of materials. For instance, lipids such as monoglycerides, triglycerides, glycerophospholipids and middle- and short-chains fatty acids are used in the formulation of lipophilic matrix tablets, self-microemulsifying DDS, solid lipid nanoparticulate DDS and nanostructured lipid carriers, among others. It is noteworthy to mention that middle- and short-chains fatty acids are able to reversibly destabilize the tight junctions of the epithelium, and thereby enhancing intestinal permeability of the loaded drug [17,18].

3. Formation and degradation of silica

Silica can be classified in two main categories, crystalline (*i.e.* quartz, cristobalite, tridymite or calcinated diatomite) or amorphous, as a function of the connectivity between the tetrahedral units and of the long-range periodicity in the network. Fig. 1 illustrates typical differences of periodicity between an amorphous bulk silica and cristobalite, chosen as example of crystalline silica. In both cases, the bulk of silica is composed of SiO_4 tetrahedral units that form siloxane rings of different Si–O sizes. The size of the silica rings present on the silica surface generally ranges from flexible 12-membered rings to strained 4-member Si–O rings and the distribution of such siloxane rings generally depends on the calcination/activation temperature of silica [19]. At the surface, different kinds of silanols can be found; they can be classified as isolated (non-H-bonded), geminal, vicinal, and interacting (H-bonded) silanols (Fig. 2). In the case of crystalline silica, such as cristobalite, only three kind of silanols can be found at the surface: geminal (for 001 termination), vicinal (for 101 termination) and isolated silanols (for 111 termination), while in the case of amorphous silica all kind of silanols are found. This property explains the highest reactivity of amorphous silica surface *vs* cristalline ones. Moreover, depending on the reaction conditions, such as temperature or condensation degree, the OH density at the surface of the material can be tuned between less then 1 to 7 OH/nm^2.

For oral drug delivery applications only amorphous silica should be considered, due to its lower toxicity and increased dissolution in biological fluids. Amorphous silica can be classified in natural (biosilica, *e.g.* diatomite) and synthetic (Fig. 3). In the last category various forms of silica were defined depending for example on the process: wet, *i.e.* silica-gel, precipitated and colloidal silica and thermal, *i.e.* fused and fumed silica.

There are four types of silica-based materials used as oral delivery systems: (1) non-porous silica nanoparticles (fumed or Stöber nanoparticles), (2) mesoporous silica nanoparticles, (3) mesoporous silica based materials, (4) biosilica, *e.g.* diatoms. Payload materials can be obtained either by post silica synthesis or by one pot synthesis. These materials can be obtained at low temperature, which is compatible with the manipulation of drugs, biomolecules [20] or cells [21].

3.1. Synthesis of non-porous silica nanoparticles

3.1.1. Fumed silica nanoparticles

Amorphous fumed silica is manufactured through a flame-synthesis technology in which silicon tetrachloride ($SiCl_4$) playing the role of precursor is vaporized in an oxygen-hydrogen flame. The spontaneous and quantitative hydrolysis reaction with oxygen and hydrogen is giving