EXPERT OPINION

Inorganic matrices: an answer to low drug solubility problem

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Introduction: Many active pharmaceutical ingredients (APIs), in development and already on the market, show a limited and variable bioavailability mainly associated to inadequate biopharmaceutical properties such as aqueous solubility and dissolution rate. The latter is the main factor responsible for the limited, and sometimes inadequate, efficacy of many orally administered drugs, belonging to class II and IV of the Biopharmaceutics Classification System (BCS). Moreover, because of their low solubility, such drugs require high doses to be administered in order to obtain their pharmacological effect, increasing the side effect incidence.
Areas covered: The present review reports the most common technological approaches intended to improve solubility and dissolution rate of BCS class II and IV drugs such as nanocrystals, solid dispersions, cyclodextrins and solid lipid nanoparticles. Particular attention will be focused on the use of inorganic matrices (lamellar anionic clays and mesoporous materials) as host for the delivery of poor soluble APIs (guest).
Expert opinion: The employment of inorganic matrices for the realization of host–guest composites is a suitable strategy for the biopharmaceutical properties enhancement. This objective can be achieved without any modification of API chemical structure.

Keywords: BCS, dissolution rate, hydrotalcite, inorganic matrices, mesoporous materials, solubility

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1. Introduction

1.1 Drug solubility and dissolution

Despite the massive increase in R&D investments for the discovery of new drugs, the number of molecules reaching the market is decreasing and the poor oral bioavailability is the most considerable cause responsible for this trend [1]. Many studies highlighted that the poor solubility is the main factor responsible for low drug bioavailability [2,3].

Current literature suggests that up to 90% of new chemical entities (NCEs) in development suffers from poor aqueous solubility [4,5], responsible for their falling during preclinical and clinical trials, as well as 40% of drugs available on the market [6].

Solubility is a physicochemical property defined as the maximum amount of the most thermodynamically favored crystalline form of a molecule able to stay in solution at fixed volume of solvent, temperature and pressure, under equilibrium conditions. This equilibrium balances the solvent–solvent and solute–solute energy against solvent–solute energy [7]. The European Pharmacopoeia (Ph. Eur. VII ed.) defines solubility as solvent parts (ml) necessary to dissolve one part (g) of solute at 25°C and active pharmaceutical ingredients (APIs), classified as poor soluble, usually show a solubility < 100 µg/ml [8]. The solubility of a substance is a static property that represents a critical determinant of its dissolution rate. Dissolution

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Article highlights.

- Many active pharmaceutical ingredients show a limited and variable bioavailability mainly associated to inadequate biopharmaceutical properties.
- The problem of low solubility can be overcome by a suitable delivery system.
- Technological approaches should be the most appropriate strategy in poor solubility enhancements as the drug chemical structure is not modified.
- Inorganic matrices represent an interesting tool for the drug solubility enhancement.
- Inorganic matrices are able to store drug into nanometric galleries or pores in non-crystalline form; in this way rapid dissolution can occur after the contact with dissolution medium.

This box summarizes key points contained in the article.

is defined as the process by which a solid enters in the solvent to yield a solution [9]. Once in contact with the dissolution medium, the drug rapidly saturates the adjacent fluid volume creating a diffusion layer. Drug molecules diffuse from the layer to the bulk and immediately replaced in the layer from the solid surface. Noyes-Whitney equation, modified by Nernst and Brunner [10] (Eq. 1), describes dissolution kinetic and underlines that the difference between drug saturation solubility (C_s) and its concentration in the bulk fluid (C_g) represents the driving force for dissolution.

$$dC/dt = \left[\frac{D \cdot A}{V \cdot h}\right] \cdot \left(C_s - C_g\right) \quad \text{(Eq.1)}$$

dC/dt = rate of drug dissolution at time t;
D = diffusion coefficient;
A = surface area of drug particles;
V = volume of the dissolution medium;
h = thickness of the diffusion layer;
C_s = saturation solubility of the drug under luminal conditions;
C_g = concentration of drug in the bulk solvent.

The main reasons influencing drug dissolution are: i) physicochemical parameters [8], ii) physiological parameters [11] and iii) formulation and manufacturing variables (**Table 1**) [9].

1.1.1 Physicochemical parameters

The main factors conditioning the amount and rate of drug dissolution (**Table 1**) are the physicochemical properties: *pKa* [12], c*rystalline state* [13], *wettability* [14] and *hydrophilicity*.

1.1.2 Physiological parameters

These variables are very numerous (**Table 1**) and are represented by biological fluid composition and GI hydrodynamics [15], food presence [16], GI fluid pH [17], age and phenotypic differences.

1.1.3 Formulation composition and manufacturing variables (Table 1)

Powders, granules, tablets and capsules are the main pharmaceutical dosage forms for oral administration. For a drug administered as solid dosage form, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence of events responsible for the complete availability at the absorption site. Disintegration and deaggregation refer to the passages necessary to obtain the drug dissolution starting from a tablet. The disintegration rate of the dosage form and the size of the particles, deriving from this process, can represent the rate-limiting step of the dissolution process. After administration, the dosage form gets in contact with the GI fluids and disintegrates, generating large particles, which must deaggregate to yield fine particles able to offer a large surface area to GI fluids giving rise to a high amount of dissolved drug, available for absorption [9], according to Nernst and Brunner equation. In compliance with this theory, the dissolution rate is directly proportional to drug surface area, more precisely to drug particles exposed to GI fluids [18]. This means that the drug–medium interactions increase as particle size decreases confirming that API particle size is an important parameter influencing drug dissolution. For this reason it is important to consider that sometimes the manufacturing procedures (e.g., granulates) could affect drug dissolution in terms of particle wettability and surface area. Another important factor is represented by the compression force, which influences API apparent density, porosity, hardness, primary particle size and disintegration time [9].

The kind and the amount of excipients employed for preparation of dosage forms play an important role in drug liberation from formulations [19]. Diluents, fillers, granulating agents, disintegrants and lubricants can condition drug wettability, particle size and the effective exposed surface area, increasing or reducing the hydrophilic characteristics of the API. Interactions between drug and excipient could occur during the manufacturing process bringing to a different dissolution profile in comparison to the drug alone [9].

2. The Biopharmaceutics Classification System

The discovery of the important role that solubility, dissolution rate and permeability play in conditioning the orally administered drug bioavailability represents the base for the development of the Biopharmaceutics Classification System (BCS). In 1995, Amidon proposed two models in order to develop *in vitro* tests able to individuate a relationship between drug solubility, dissolution and absorption properties [20]. The models allow the identification of the parameters controlling drug dissolution and absorption [20], expressed as: *Absorption Number, Dose Number* and *Dissolution number*.

The Absorption Number (An), related to drug GI permeability, is described as the product of permeability (P_{eff}) and the gut radius (R) ratio and the residence time (T_{si}) in the

Table 1. Main parameters influencing drug dissolution in the GI tract.

Physicochemical parameters	pKa Crystalline state Wettability Hydrophilicity
Physiological parameters	Viscosity of lumenal contents Motility patterns and flow rate pH and GI composition GI permeability and presystemic metabolism. Secretion, co-administered fluids Intra and inter-individual variations Age, weight, disease states
Formulation and manufacturing variables	Nature of the dosage form (solutions, suspensions, capsules, tablets, coated tablets, controlled-release formulations) Particle size Amount and kind of excipients Compression force

small intestine. *An* can be also written as the ratio of residence time (T_{si}) and absorptive time (T_{abs}) (Eq. 2).

$$An = \left(\frac{P_{eff}}{R}\right) T_{(si)} = \left(\frac{T_{si}}{T_{abs}}\right) \quad \text{(Eq.2)}$$

Permeability depends upon transport across GI wall at the site of absorption; in fact, the drug must be in solution and has to be in contact with the site for an adequate time in order to guarantee the absorption of a large amount of API. Many methods can be used to determine permeability: i) *in vivo* human intestinal perfusion, ii) *in vivo* or *in situ* animal intestinal perfusion, iii) *in vitro* excised human or animal intestinal tissue and iv) *in vitro* cultured epithelial cell monolayer (i.e., Caco-2 cells). Active pharmaceutical ingredients are classified highly permeable when the extent of intestinal absorption is > 90% of the administered dose [21]. In this case they show a high absorption number (*An* > 1) [22].

The *Dose Number (Do)*, function of drug solubility, is defined as the ratio of dose concentration (M/V_o, where M is the highest dose strength and V_0 = 250 ml) to drug solubility (C_s) (Eq. 3).

$$Do = \frac{M/V_o}{C_s} \quad \text{(Eq.3)}$$

Solubility is determined reproducing physiological conditions, in terms of pH values and temperature, by the saturation shake-flask method. Single solubility values are inadequate for the classification because of its static characteristic, not suitable to describe adequately dissolution process of the entire administered dose. For this reason solubility is determined by dose/solubility ratio (D/S) [23]. For low *Do* values, drug substances are considered highly soluble because the highest dose strength is soluble in 250 ml (derived from bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water) or less of aqueous media between pH 1.0 and 7.5 at 37°C [21]. On the contrary, poorly soluble drugs show a high *Do* value, meaning that the dose concentration exceeds solubility.

The *Dissolution Number (Dn)*, function of drug release from formulation, is the ratio of the residence time (T_{si}) and the dissolution time (T_{diss}), which includes solubility (C_s), diffusivity (D), density (ρ) and the initial particle radius (r) of a compound, and the residence time (T_{si}) (Eq. 4).

$$Dn = \left(\frac{3D}{r^2}\right) \cdot \left(\frac{C}{\rho}\right) \cdot T_{si} = \frac{T_{si}}{T_{diss}} \quad \text{(Eq.4)}$$

Dissolution tests are performed in USP Apparatus I at 100 rpm (basket method, generally used for floating formulations as capsules) or USP Apparatus II at 50 rpm (paddle method, generally employed for tablets) in a volume of 900 ml of various pH values by using different dissolution media (simulated gastric fluid without enzymes pH 1.2, buffer pH 4.5 and simulated intestinal fluid without enzymes at pH 6.8). An API dissolves rapidly when not less than 85% of the total amount administered dissolves within 30 min (high *Dn* value) [21]. After analysis of these parameters, the BCS classifies orally administered drugs into four classes as follows [20].

Class I: high soluble–high permeable drugs, that is, metronidazole and diazepam [21]. These compounds dissolve rapidly and are well absorbed guarantying a reproducible blood concentration. The absorption rate is controlled by gastric emptying. For these molecules it is possible to obtain an *in vitro–in vivo* correlation (IVIVC).

Class II: low soluble–high permeable drugs, that is, carbamazepine, griseofulvin and nimesulide [21]. Compounds of this class exhibit low solubility and high permeability, showing that the step limiting absorption rate is the dissolution time. Generally it depends on physicochemical characteristics of the drugs and on the GI environment conditions.

Class III: high soluble–low permeable drugs, that is, acyclovir and captopril [21]. The bioavailability of these molecules is not reproducible because of the combination of physiological factors and biopharmaceutical properties (GI motility, permeability, metabolism, dissolution and interaction/binding of drugs with excipients) influencing absorption kinetics.

Class IV: low soluble–low permeable drugs, that is, furosemide [21]. These compounds exhibit a lot of problems for effective oral administration because of poor solubility in biological fluids and low ability to pass biological membranes.

3. Pharmaceutical approaches for drug dissolution rate enhancement

In recent years, many efforts have been made by numerous research groups to solve the problems of low oral bioavailability of poor soluble APIs by enhancing their dissolution rate

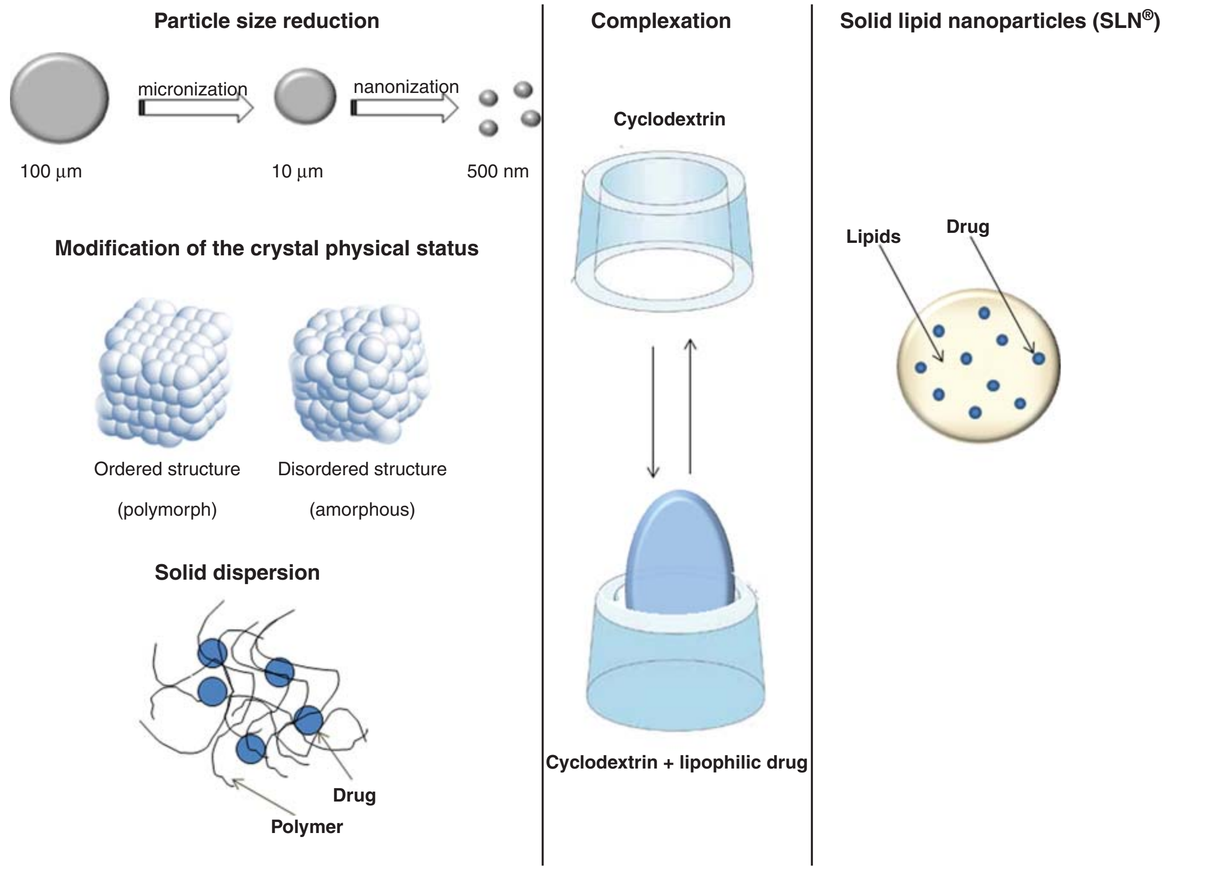

Figure 1. Schematic representation of the main technological approaches for drug dissolution enhancement.

(**Figure 1**) [24]. One of the early and common approaches used is represented from particle size reduction. The increase of surface area, due to particle size reduction, improves drug dissolution according to Nernst and Brunner equation (Eq. 1). This phenomenon can be explained considering that, decreasing the size, particle curvature can increase dissolution pressure, leading to an increase of the saturation solubility around the particle [25]. Particle size reduction can be achieved by micronization using milling processes or spray drying, precipitation from supercritical fluid, controlled crystallization through which the coarse drug powder is converted to an ultrafine powder with a mean particle size typically in the range of 2 – 5 µm [26].

In recent years, a further evolution in particle size reduction practice has been introduced by nanocrystal technology. Nanocrystals are nanoparticles constituted by drug with a mean particle size below 1 µm [27]. An important feature of drug nanocrystals is the increase of drug dissolution rate through the increased surface area and saturation solubility [25]. The main limit of this strategy is the narrow field of application as it can be applied only for drugs with a low oral single dose. In fact, the main problem deriving from high amount in the same single dose is that the particles can get in contact with each other and might fuse forming larger crystals under the compression pressure (during tablet manufacturing) or during storage conditions. The crystal dimensions changes induce the modification of drug pharmacokinetic profiles in comparison to nanocrystals in the original formulation [27].

Another approach exploits the principle that pharmaceutical solids can exist in different physical status forms, such as crystalline (polymorphs), amorphous, solvated or hydrated states (**Figure 1**) [28]. Thus, a drug can exist in different polymorphic forms which are crystalline forms differing in molecular packing, physicochemical properties such as shelf-life, melting point, vapor pressure, solubility, morphology and density. The most stable polymorphic form of a drug is often used to prepare dosage forms because it has the lowest potential for conversion from one polymorphic form to another. The amorphous form differs from the other as it does not display any long-range translational orientation symmetry, characterizing crystalline structures. The amorphous form requires minimal energy for breaking, once in contact with the dissolution medium in comparison to the corresponding crystalline form due to absence of an ordered crystal lattice, providing a higher solubility. However, amorphous systems are characterized by limited physical stability and high chemical reactivity. In regard to this last aspect, the realization of solid dispersions represents an interesting approach (**Figure 1**).

Solid dispersions are described as mixtures of poor water-soluble drugs (which can be dispersed molecularly, in amorphous or crystalline particles) in hydrophilic carriers that control the release kinetic [29]. The solid dispersions are projected with the aim to improve the dissolution rate by increasing the specific surface area for effect of drug dispersion in the carrier, in molecular form or as small particles. In regards to the latter, the particle size reduction brings to powder agglomerate formation. Whereas, dispersing the compound in a carrier, it is possible to increase solubility maximizing API surface area coming in contact with the dissolution medium as the carrier dissolves and avoiding, at the same time, the change of the original particles' physical status [30]. Drug amorphization and stabilization of this form can be achieved also by its co-grinding with excipients [31,32]. By this technique the amorphous form is stabilized by the interactions established with the co-grinded material (e.g., cyclodextrins, inorganic materials), preventing the conversion into the most thermodynamically stable polymorphic form. However, this method is not suitable for thermolable drugs as heath production occur during grinding procedure.

An emerging approach in drug dissolution enhancement is represented by the complexation of poor soluble drugs with hydrophilic carriers such as cyclodextrins (CDs) (**Figure 1**) containing six (α-CD), seven (β-CD), eight (γ-CD), nine (δ-CD), 10 (ε-CD) or more (α-1,4)-linked α-D-glucopyranose units. Cyclodextrins show a typical shape of a truncated cone or torus due to the chair conformation of the glucopyranose units. Because of their lipophilic inner cavity, CDs can form inclusion complexes with many poor water-soluble organic molecules forming host–guest supramolecular complexes [33]. Despite the large use of such carrier for the delivery of poor soluble drugs, some limitations can be found. One of them is that CDs are not able to store large molecules and CDs with larger cavities are required. These kinds of systems are thermodynamically instable and expensive to prepare [33].

In recent years, lipid-based delivery systems (**Figure 1**), suitable for highly lipophilic APIs [34] have been introduced. Self-emulsifying lipid-based formulations [35] and solid lipid nanoparticles (SLN®) are an example of such systems [36]. The increase of drug dissolution depends on the presence of exogenous lipids in the duodenum suitable to stimulate the secretion of biliary lipids able to combine to lipid digestion products to generate a series of colloidal species including micelles, mixed micelles, vesicles and emulsion droplets [37].

In recent years, many types of inorganic materials have attracted considerable attention for the realization of new delivery systems able to improve drug solubility and dissolution. Among the matrices suitable for such application, ordered mesoporous silica materials [38] and layered double hydroxides [39,40] found considerable attention. The use of inorganic materials as drug devices results advantageous as they show a high chemical and mechanical stability and low susceptibility to microbiological contamination. These materials are able to act as host for organic molecules (guests) such as drugs, forming inorganic–organic hybrids [39-43].

3.1. Ordered mesoporous silica materials

According to IUPAC definition, porous materials are classified into three groups [44] in relation of pore diameter:

- microporous: < 2 nm,
- mesoporous: between 2 and 50 nm,
- macroporous: > 50 nm.

The ordered mesoporous silica materials (OMS) are characterized by highly ordered and stable porous structure, large pore size and well-defined surface properties. Because of these properties, OMS found application as host materials for drugs. The OMS family offers different matrix type with different pore size enabling them to entrap both large and small molecules [45]. The first OMS, M41S family, was developed in the early 1990s by the scientists of Mobil Oil Corporation [46] and the first mesoporous solid synthesized with regularly ordered pore arrangement and very narrow pore distribution was MCM-41, discovered in 1992 [47]. This family of materials is characterized by hexagonally arrays of cylindrical mesopores, narrow pore size distribution, generally from 1.5 to 10 nm, and high surface areas (above 700 $m^2 g^{-1}$). The pore wall structure consists of a disordered network of siloxane bridges and free silanol groups [48] that could act as reacting nuclei for molecule binding and for derivatization. This last aspect is important because the possibility to modify the surface characteristics through functionalization in order to make these materials able to store molecules with different lipophilicity/hydrophilicity degree and to obtain a controlled release [49]. MCM-41 is synthesized by self-assembling silica and surfactant (usually quaternary ammonium salts) micelles used as structure-directing agents responsible for the hexagonal array and parallel organization of pore channels.

Several studies investigated the building mechanism of MCM-41 and the 'liquid-crystal templating' (LCT) mechanism [50] suggested by Beck *et al.* [51] seems to include all these proposed mechanisms. These authors proposed two main pathways, in which either the liquid–crystal phase is intact before the silicate species are added, or the addition of the silicate results in the ordering of the subsequent silicate-encased surfactant micelles. The cooperative action between the negatively charged silicate species and the positively charged quaternary ammonium micelles leads to the ordered structure of these materials. The surfactant is removed by calcination, leaving the porous silicate network. During calcination, de-hydroxylation of hydrogen-bounded and geminal silanol groups occur upon formation of siloxane bonds and this generates an increase of single silanol groups. The remaining geminal and single silanols are highly accessible and can interact with appropriate organic functional groups such as those commonly present in drugs. These physical interactions allow the adsorption of hosts in the mesopores surface and their release in proper conditions.

In 1998, a new family of highly OMS was synthesized in an acid medium by the use of commercially available non-ionic triblock copolymers ($EO_nPO_mEO_n$) with large polyethyleneoxide $(EO)_n$ and polypropyleneoxide (PO)m blocks [52]. Different materials with a diversity of periodic arrangements have been prepared and named SBA materials (the acronym for Santa Barbara Acids). A wide variety of SBA materials has been reported in the literature, such as SBA-1 (cubic), SBA-11 (cubic), SBA-12 (3D hexagonal network), SBA-14 (lamellar), SBA-15 (2D hexagonal) and SBA-16 (cubic cage-structured) [53]. Among them, SBA-15 immediately attracted a lot of attention for the application in drug delivery field. SBA-15 silica is a combined micro- and mesoporous material with hexagonally ordered tuneable uniform mesopores (4 – 14 nm) [54]; it exhibits attractive features, including large mesopore size and volume, high-specific surface area and connectivity between adjacent mesopores through pores (micropores and narrow mesopores) present in the walls of the primary (ordered) mesopores.

The micropores generate from the penetration of the hydrophilic poly(ethylene oxide) chain from the triblock copolymer template into the silica framework [55]. SBA-15 consists of thick microporous silica pore walls (3 – 6 nm) responsible for the high hydrothermal stability of SBA-15 compared to other mesoporous materials with thin pore walls like MCM-41 (Mobil Composition of Matter), MCM-48 (Mobil Composition of Matter), HMS (hexagonal mesoporous silica) [56]. From SEM analysis results that SBA-15 shows particles of dimensions lower of 5 µm, some of them characterized by hexagonal morphology, and organized as small aggregates. Moreover X-ray diffraction patterns of the SBA-15 materials reveal the 2-D hexagonally structured pores (p6 mm space group) at low angles.

3.1.1 *Use of mesoporous materials in drug solubility enhancement*

The antiepileptic drug carbamazepine (CARBA), classified as BCS class II drug, and the diuretic furosemide (FURO) belonging to BCS class IV, were included in the mesoporous silica MCM-41 [57,58]. Both molecules were absorbed into MCM-41 pores, by the adsorption method [59], in which the matrix was immersed into a saturated drug solution until equilibration and the loading products were recovered by filtration. The X-ray diffraction patterns (XRPD), registered for the final inclusion products MCM-41-CARBA and MCM-41-FURO, showed the same profiles of the raw matrix MCM-41. This observation is an important starting point in the employment of such materials for drug dissolution enhancement. In fact, as the XRPD spectra of MCM-41-CARBA and MCM-41-FURO do not show typical reflex of the corresponding crystalline drug, it means that, once adsorbed into MCM-41 pores, APIs are not organized as crystals. This observation was also confirmed by the thermal profiles registered for both inclusion products that did not show peaks attributable to drug melting, clearly visible for crystalline drugs alone.

For poor soluble drugs, as CARBA and FURO, the crystal lattice disruption represents the rate-determining step of dissolution. The inclusion of such drugs into MCM-41 pores is an interesting approach in the attempt to overcome this limitation as the adsorbed drug is not organized in crystals. The suitability of this technological approach is confirmed from the release studies that reveal the enhanced release of CARBA and FURO from the corresponding inclusion products in comparison to the controls (crystalline CARBA or FURO alone or physically mixed to MCM-41) (**Figure 2** and **Figure 3**).

The improvement of drug release is based on two important features of the inclusion products: the first one is the lack of crystals, the second one is that, during the loading procedure, the drug molecules establish light interactions with the terminal silanols of MCM-41 (hydrogen bonds). Thus, once in contact with the dissolution medium, such interactions can be easily broken and the drug can be rapidly available to be absorbed.

Actually, many mesoporous materials, with different characteristics, are available to be used as carrier for the delivery of orally administered drugs such as porous silicon (PSi), thermally carbonized porous silicon (TCPSi), SBA-15 and TUD-1 (Technische Universiteit Delft) [60]. These matrices show characteristics that make them suitable to be used for APIs with different characteristics.

In the case of MCM-41-FURO inclusion product, despite the satisfying results obtained in terms of release enhancement, a very low drug loading was obtained (~ 3.0%); this represents a strong limit to the application in therapy of such system. The low drug loading can be explained considering that, probably, FURO molecules orientate themselves inside the pores, during the loading procedure, creating an obstruction for further molecule adsorption. Moreover, MCM-41 pore dimensions (diameter 3.32 nm) are not suitable to load a high amount of large molecules as FURO (length 1.2 nm). In this context it was useful to prepare a new inclusion product of FURO by means of a mesoporous matrix, such as SBA-15, with larger pores than MCM-41. Thus a new inclusion product, SBA-15-FURO, has been prepared reaching a final loading of 30% (10 times more than MCM-41-FURO) obtaining, also in this case a significant improvement of FURO release (**Figure 4**) [58].

The use of mesoporous systems in the dissolution enhancement is advantageous as the drug adsorption is performed by methods that do not modify API chemical structure. It must be underlined that the physical status of included drug characterized from stability; however, physical stability studies, performed along 6 months in stressed conditions of temperature and humidity (40°C, 75% RH), demonstrated that the drug confined into pores is physically stabilized. These findings can be explained by literature data indicating that re-crystallization of molecules included into

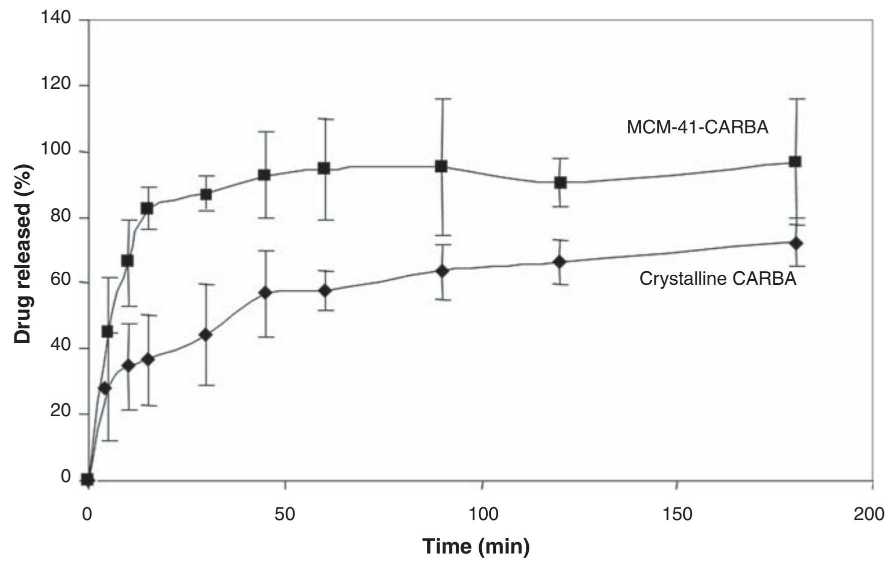

Figure 2. Release profiles of crystalline CARBA and MCM-41-CARBA in gastric fluid pH 1.2 at 37.0°C ± 0.5 (n = 5 ± SD).
Reproduced from [57] with permission of Elsevier.

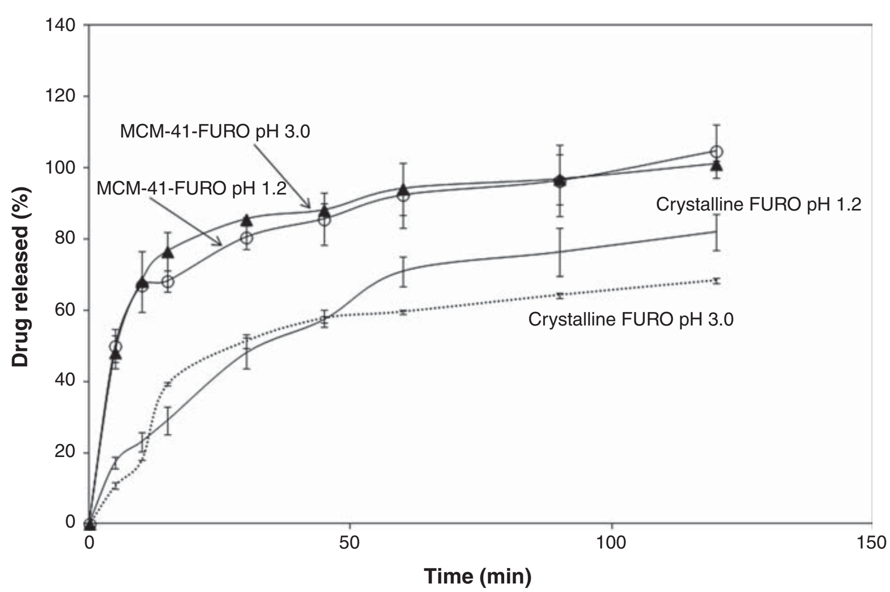

Figure 3. Release profiles of crystalline FURO and MCM-41-FURO in gastric fluids pH 1.2 and 3.0 at 37.0°C ± 0.5 (n = 5 ± SD).
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the pores occurs only when the pore size is more than 20 times the size of the molecule [61]. Thus, comparing MCM-41 and SBA-15 pore size (an average of 3.32 and 7 nm, respectively) with FURO molecular size (1.2 nm length) it is possible to assess that the drug is confined in a nanosized space that prevents its re-crystallization.

3.2 Hydrotalcite-like compounds (HTlcs)

Hydrotalcite-like anionic clays (HTlc), also known as layered double hydroxides (LDHs), are the most representative of the anionic clays family. These are natural and synthetic lamellar mixed hydroxides with interlayer spaces containing exchangeable anions [62].

HTlcs show a lamellar structure; each lamella is similar to brucite $Mg(OH)_2$, which crystallizes in a layer-type lattice as a consequence of the presence of relatively small positively charged divalent cations in close proximity to the non-spherosymmetrical and highly polarizable OH^- ions. Each Mg^{2+} ion is octahedrally surrounded by six OH^- ions and the different octahedral share edges to form infinite sheets.

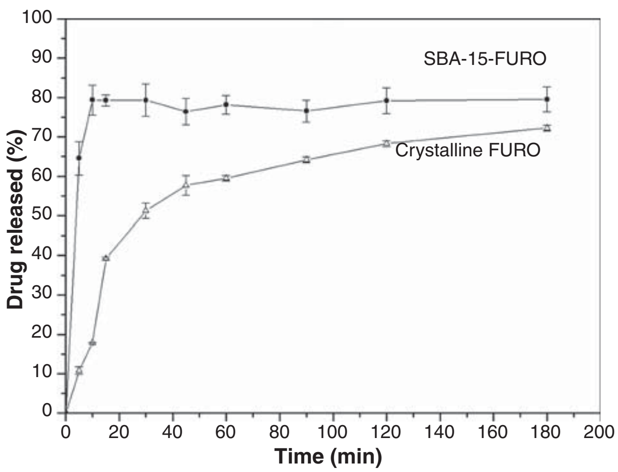

Figure 4. Release profiles of crystalline FURO and SBA-15-FURO in gastric fluid pH 3.0 at 37.0°C ± 0.5 (n = 5 ± SD).
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The sheets are stacked one on top of the other and are held together by weak interactions through hydrogen atoms [62]. The replacement of some divalent cations with those of higher charge (such as Al^{3+}, Fe^{3+}, etc.) makes the sheet positively charged and the electrical neutrality is maintained by counteranions located in the interlayer space [62].

HTlcs are present in nature, not in large quantity, but they can be easily synthesized in laboratory at high level of purity, moreover are cheap, eco-compatible and can be organically modified with a variety of organic anions [62,63].

HTlcs have general formula $[M(II)_{1-x}M(III)_x(OH)_2]^{x+}(A^{n-}_{x/n})^{x-}$ mS, where M(II) is a divalent metal cation (usually Mg, Zn), M(III) is a trivalent metal cation (usually Al, Fe), generally M(II)/M(III) = 2, A^{n-} is an exchangeable inorganic or organic anion, and m are the moles of solvent S, usually water, co-intercalated per mole of compound.

An intercalated anion can be replaced by via ion-exchange mechanism, with consequent variation of the interlayer distance. The diffusion of anionic species with high steric hindrance into the interlamellar region will be facilitated if the counterion is little held and determines a large gallery height. There is a scale of selectivity for the most common counteranions: $CO_3^{2-} > SO_4^{2-} > OH^- > F^- > Cl^- > Br^- > NO_3^- > ClO_4^-$ [64,65]. HTlc containing chloride, or rather, nitrate anions are the most suitable precursors for biologically active species uptake.

Because of their properties, HTlcs found numerous applications in many fields as catalysts and catalysts' precursors [66], in the preparation of pigments [67], in the removal of waste agents from water [68], in pharmaceutical field [39] as excipients in cosmetics [69], as rheology modifiers [70] for the symptomatic treatment of peptic ulcers [71] and for the therapy of digestive disorders as well as drug [72] and biomolecule host [73,74].

In recent years, HTlcs knew a growing interest as drug delivery systems (DDS) due to their host–guest type structure acting as host material in which many anionic molecules (guests) as biologically active compounds could be stored. HTlcs show a high versatility and can be used to develop systems able to promote both systemic [75-79] or specific targeted delivery [80,81].

As discussed before, only anionic molecules are eligible to be intercalated. Generally, the salt form of the drug/biomolecule is used because in this way it can dissociate in aqueous solution generating the free anionic form suitable to be intercalated between HTlc lamellae, by anion exchange. Once intercalated, drug molecules are not organized as crystals and give rise to a new nanostructured product in which the drug (guest or internal phase) is molecularly dispersed in the nanospaces of HTlc interlayer region (host or external phase) forming a 'shell-liquid state'.

HTlc results a suitable material to be used for *in vivo* drug delivery and, at the same time, it can provide additional benefits. The confinement of the drug molecules between the metal hydroxide layers is responsible for drug isolation from the environment thereby improving long-term stability and storage, especially because many molecules are instable in certain conditions [82,83].

HTlcs show many interesting properties, making them a good material to develop new pharmaceutical formulations, as: i) biocompatibility [84], ii) high drug loading, iii) stability to thermal treatments, iv) stabilizing agent for photolable molecules [85-88], v) good compactability and tableting properties in dry conditions [89] and vi) excipient able to improve the solubility of poorly soluble drugs [90,91].

3.2.1 *Use of hydrotalcite-like compounds in drug solubility enhancement*

The use of HTlcs as host materials for poor soluble drugs is an interesting approach in order to improve API dissolution, once in contact with the dissolution medium. The rate-determining step of poor soluble drugs dissolution is represented by the high energy and time required for crystal lattice disruption. The intercalation of low soluble drugs into the HTlc lamellae has the advantage to generate a final composite in which the drug (guest) is present in molecular form between the interlayer space because of crystal structure loss. The molecules, in anionic form, bind HTlc lamellae (host) by ionic interactions established with the M(III) positive charge. After the contact with the dissolution medium, drug molecules are released by ion exchange with Cl^- and PO_4^{3-} anions present in the fluids (gastric, intestinal). Moreover, at low pH values (< 4.0) HTlc undergoes to gradual disruption promoting drug molecules' release. Thus, once released, the drug is ready to be absorbed and to reach the action site obtaining a more rapid therapeutic effect, compared to the traditional formulations in which the drug is present in crystalline form.

The benefits in drug dissolution enhancement have been demonstrated from numerous studies. The family of anti-inflammatory drugs (NSAID) has been largely investigated

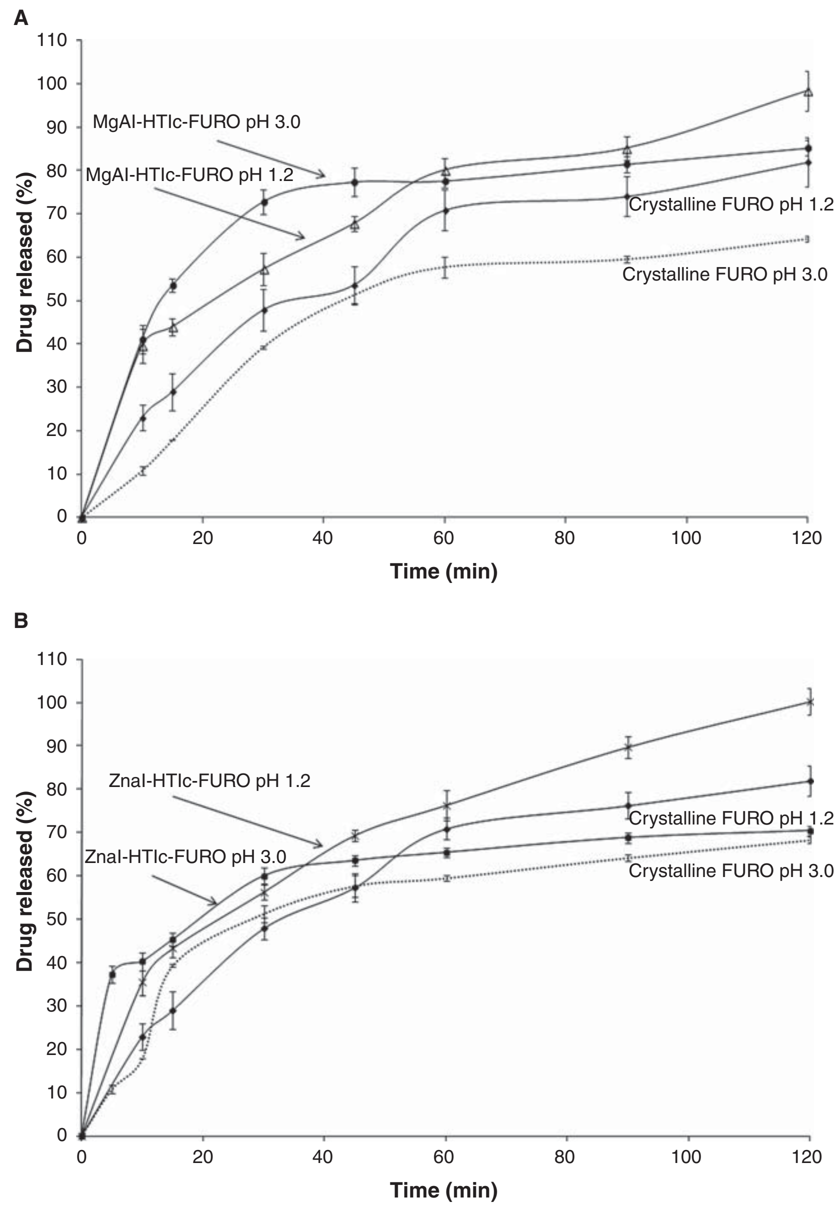

Figure 5. A. Release profiles of crystalline FURO and the intercalation product MgAl-HTlc-FURO and **B.** FURO and the intercalation product ZnAl-HTlc-FURO in gastric fluids pH 1.2 and 3.0 at 37.0°C ± 0.5 (n = 5 ± SD).
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for the development of HTlcs composites. Indomethacin (INDH) [90], tiaprofenic acid (TIAPH) [90], propionic acid, ketoprofen (KETH) [90], diclofenac (DIK) [80,92], ibuprofen (IBU) [75], flurbiprofen (FLUR) [89,91], belonging to BCS class II, are characterized from low solubility and are good candidate for DDS able to increase their dissolution rate [75,79,80,90-93].

Active pharmaceutical ingredient molecules must be in anionic form in order to be stored in HTlc galleries, as reported above. The drugs previously mentioned show an acidic nature due to the –COOH group that can be easily salified to obtain the anionic form. Thus, the intercalation procedure starts with the preparation of a drug suspension, in carbon dioxide-free water, to which a carbon dioxide-free NaOH (1 M) water solution is added obtaining a sodium salt solution of the drug. At this point, the pristine HTlc (e.g., HTlc-Cl) is added to drug sodium salt solution and then stirred for an established time. During this period the drug molecules exchange with Cl^- anions stored in the starting HTlc and their intercalation into HTlc galleries produces an increase of the interlamellar space due to the high dimensions of such molecules in comparison to Cl^-. This aspect is well highlighted by X-ray pattern (XRPD) of HTlc-Cl and the corresponding intercalation products. Moreover, such analyses allow to affirm that, once intercalated, the drug molecules are not organized as crystals as the pattern of each composite does not show reflex attributable to drug crystalline form. These observations can be confirmed by DSC analyses too. By submitting the intercalation composites to *in vitro* release studies and comparing their profiles with that coming from the drug crystalline form, or physically mixed to the pristine HTlc-Cl, resulted that the composites are able to release a higher amount of drug in comparison to the corresponding crystalline forms.

It is well known that one of the most common adverse effects of NSAIDs is represented from gastroduodenal mucosa damage. As NSAIDs are among the most widely used products in the treatment of moderate pain and fever, it is important to preserve the patients from gastrolesivity associated to NSAIDs administration. One of the strategies proposed to reduce gastric mucosal damage is represented by a gastroprotective therapy in all patients receiving NSAIDs [94]. The use of NSAIDs as HTlc composites combines the anti-inflammatory effect of the intercalated molecules to a protective action toward gastric mucosa exerted from HTlc. Previous studies, in fact, suggested that HTlc has barrier properties similar to those of gastric mucus. It is noteworthy that at low pH values (< 4.0) HTlc destruction [95] forming a gel-like structure able to adhere on mucosal surface and to afford protection mimic the barrier properties of gastric mucous gel [96,97].

The advantage in the use of HTlc has been demonstrated in the delivery of BCS class IV drugs as the diuretic furosemide (FURO) [93] also. FURO, because of its weak acidic nature, is preferentially absorbed in the stomach [98] site in which it displays its lowest solubility [99]. The intercalation of such molecule into the lamellae of ZnAl-HTlc and MgAl-HTlc generates new nanostructured products in which FURO is not organized as crystals, but as molecular film, as showed in XRPD patterns and DSC profiles (data not reported).

The intercalation products ZnAl-HTlc-FURO and MgAl-HTlc-FURO are able to improve FURO release at acidic pH values: 1.2 and 3.0. The enhancement of FURO amount released in such conditions can be ascribed to i) the immediate availability of drug molecules stored in the interlayer space that can be easily exchanged by anions of the gastric fluids (as: Cl^-) and ii) as consequence of the low pH (< 4.0), HTlc undergoes to gradual destruction of its lamellar structure and its dissolution [95] promoting the release of the intercalated molecules.

The obtained results suggest that the intercalation is able to improve FURO release in a medium in which it is low soluble (**Figure 5A and B**).

The oral administration of a HTlc composite allows to obtain a rapid release in the stomach of the intercalated drug molecules mainly due to the matrix solubility in acidic media [77,91]. However, HTlc composites can be properly formulated in order to obtain an intestinal drug delivery. In fact, by the realization of gastro-resistant forms, the HTlc composite can by-pass unaltered the acidic gastric environment reaching the intestine. In this place (pH > 4.0) HTlc structure is not dissolved by intestinal medium and the drug can be gradually released, thanks to ion exchange mechanism triggered by carbonate, chloride and phosphate anions [77,91]. This approach can be useful in the treatment of pathological diseases involving a part of the intestine such as the colon [80] or to obtain a controlled release [92].

4. Expert opinion

Inorganic matrices represent a new interesting strategy in the enhancement of drug dissolution rate and solubility. Among the inorganic matrices available, considerable attention was devoted to mesoporous materials (MCM-41 and SBA-15) and lamellar anionic clays (HTlc) because of their novelty in comparison to well-known silica materials or cationic clays. Both types of matrices are synthesized in laboratory by simple, cheap and green methods easily scalable to industry. These materials, produced in laboratory, show some advantages in comparison to natural co-respective, silica in the case of mesoporous and cationic clays in the case of hydrotalcite. In fact, the natural materials show a low chemical and biological purity and this means that they must be purified (sterilization) before use. Moreover, the synthetic matrices are less amorphous and show a more organized microstructure.

The mesoporous materials and the lamellar anionic clays show a high versatility for the delivery of drugs with different physicochemical characteristics. Molecules provided of acidic groups available for ionization are required for intercalation into HTlcs, whereas the adsorption onto mesoporous materials can be achieved independently from the acidic or basic nature of the drug. The inclusion/intercalation of drugs in these matrices generates an inorganic–organic hybrid showing new properties in comparison to pristine materials (drug and matrices alone). In this new compound the drug (guest) is dispersed homogeneously in molecular form in the inorganic phase (host). The molecular dispersion of drug into the inorganic matrices generates a 'shell liquid state'. This means that, once included or intercalated, the drug is not organized as crystals and binds the matrix by light interactions that will be easily broken after the contact with the dissolution medium.

Moreover, as well described in the text, API release from a mesoporous matrix and from HTlcs follows different mechanisms. As in the mesoporous materials the drug interacts with the matrix by hydrogen bond; once in contact with the dissolution medium, drug molecules are rapidly replaced from water and high drug concentrations are easily achieved. In regards to HTlc, it can be used both to obtain an immediate release in the stomach or a specific drug release in the intestine. The first objective is achieved considering the HTlc susceptibility in acidic media. In fact, in that conditions, HTlc lamellar structure is destabilized undergoing to destruction and then dissolution promoting a quick release of intercalated drug molecules. In such conditions, the HTlc composite can be considered an API 'spring form' [100], a high-energy formulation of the drug able to generate a supersaturated state responsible for accelerated dissolution.

This is very important for APIs belonging to class II (low soluble–high permeable) and IV (low soluble–low permeable) of BCS because the solubility and dissolution rate are the main factors conditioning the efficacy of drugs. The intestinal delivery can be achieved by formulating the intercalation product as gastro-resistant form is able to by-pass the gastric environment and to reach the intestinal lumen site in which the drug is released by ion exchange mechanism.

The different nature of the two matrices allow to choose the most appropriate for the delivery of APIs showing different physicochemical properties. Moreover, both mesoporous materials and hydrotalcite can be properly modified with hydrophobic/lipophilic groups (interacting with silanol groups in the case of mesoporous materials and with the aluminum positive charge in the case of hydrotalcite) in order to make them more affine to the guest.

The realization of host–guest composites of the mesoporous materials and hydrotalcite offers numerous advantages among which the possibility to improve API biopharmaceutical properties without modification of its chemical structure. In addition, mesoporous materials and hydrotalcite are biocompatible materials for oral administration resulting safe for the patient. These characteristics can open up new possibilities for inorganic matrices, in comparison to other approaches; in the future, strategies aim to improve drug bioavailability. Particular attention could be devoted to HTlc matrix because of more interesting advantages as high drug loading and possibility to be synthesized by green methods (e.g., by using only water as solvent). Moreover, HTlc possesses antacid and gastroprotective properties, desirable characteristics for oral administration of drugs.

Drug confinement into nanometric spaces makes it more stable to physical modifications.

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