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The effect of Na_2CO_3, NaF and NH_4OH on the stability and release behavior of sol–gel derived silica xerogels embedded with bioactive compounds

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ABSTRACT

Stability, defined as the reproducible behavior of a device upon its storage, is an important issue in pharmaceutical formulation. Silica xerogels obtained through the sol–gel route are relatively new as matrices for the controlled release of drugs. In some cases, it was observed that their behavior changes upon storage, so that they cannot always be defined as "stable". This occurs especially when gel processing is performed at mild temperatures, a procedure that may have to be used to prevent degradation of the embedded drug. This work investigated the use of inorganic catalysts as potential xerogel stability inducers when gel curing by heating is not applicable. Three compounds known to accelerate sol–gel polymerization, namely ammonia, sodium fluoride and sodium carbonate, were introduced during the polymerization of low-temperature processed inorganic and organically modified gels, and the effect of each compound on xerogel stability and drug release was monitored. The use of carbonate leads to formulations with good retention properties, as opposed to ammonia and NaF, which lead to poorly retentive xerogels in accordance with their known ability to increase porosity. Ammonia was shown to be a poor stability promoter independently of gel composition, as opposed to fluoride and carbonate, which both displayed stabilizing properties in a dose-dependent manner. No correlation was found between xerogel stability and drug release properties. An attempt was also made to correlate stability data with polymerization rates and wet gel syneresis time evolution with the purpose of identifying one or more synthesis parameters that could act as stability predictors for pre-formulation studies. No correlation was found between stability and syneresis data. A similar trend in the curve of gel time vs. catalyst concentration was observed for the two stabilizing catalysts, which was different for the non-stabilizing ammonia. It was concluded that the trend of this curve could potentially provide an indicator of catalyst stabilizing efficacy.

1. Introduction

Silica is an inorganic polymer approved by the Food and Drug Administration (FDA) as an excipient in many drug formulations, well tolerated when administered both orally or topically. This material exists in different forms, depending on its preparation and processing method. One of these methods is the chemical polymerization of alkoxysilane precursors, namely the sol–gel route [1]. This procedure results in a porous and amorphous form of silica through hydrolysis and condensation of liquid or solid alkoxysilane precursors. This technique, which was originally developed for engineering applications (e.g., deposition of thin silica layers as inert or catalytic coatings), has also been extended to the preparation of matrices for the entrapment and sustained release of bioactive compounds [2–18]. One of the advantages of the sol–gel process is that it requires relatively mild conditions, often compatible with the stability of bioactive molecules which can thus be introduced in the alkoxysilane solution (sol) prior to gel formation and later remain trapped in the polymerized medium. Using this method, almost any bioactive compound can be embedded into silica gel and administered as is or as a component of more complex formulations for oral or parenteral administration.

A potential drawback of sol–gel silica is that its properties (for example, its porosity and thus drug-releasing behavior) may change upon storage [18]. Instability is mostly due to the fact that the hydrolysis and condensation reactions that lead to polymer formation are often not completed after gel formation, so that reactive silanols are still present to react at a later time [19]. In engineering and materials science applications, this instability is avoided by heating (curing) the gel (prior to or after solvent removal) at relatively high temperatures (100–500 °C). Heating completes the hydrolysis and condensation reactions and, at the same time, removes solvent residuals. However, heating at high temperature is not exploitable when thermally labile compounds,

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e.g., organic drugs, are present in the gel. In this case, the polymer must be processed at mild temperatures only (commonly <50 °C), with the consequent risk that condensation reactions do not reach completion upon drying, and the resulting xerogel is prone to further change with time. Indeed, it has been reported that mild-temperature-processed silica xerogels embedded with drugs (intended for the sustained release of the entrapped bioactive compound) display some instability upon storage. More precisely, it has been reported [18] that xerogel porosity decreases upon storage, leading to polymers with stronger retention properties. The tendency to change was shown to depend on matrix composition and/or the preparation protocol. It was also observed that the stability parameters are improved by increasing the time of wet-gel aging prior to drying, consistent with the hypothesis that condensation reactions need to be completed to obtain a stable material. To this end, long-term aging of the wet form at room temperature could be used as an alternative procedure to the heating process to promote gel ripening. However, the time of room temperature wet-gel aging necessary to obtain stable matrices was shown to be at least 15 days, too long for practical application [18]. Therefore, a procedure that shortens the time of aging is necessary in order to allow practical exploitation of these materials for biomedical applications.

This work investigated the use of catalysts as potential stability promoters, with the final purpose of reducing the time of wet aging necessary to ensure xerogel stability. To this end, three simple compounds (ammonia, sodium fluoride and sodium carbonate) known to accelerate sol–gel polymerization were selected. They were introduced at defined concentrations during the synthesis of xerogels intended for the sustained release of drugs, and their efficacy as xerogel stability promoters was evaluated.

A further purpose of this work was to identify one or more wet gel parameters during the synthesis process which could act as stability predictors before the drying step is carried out. To this end, gel time and wet syneresis were monitored as functions of catalyst type and concentration, and the information gathered was correlated with xerogel stability. The scope of this investigation had the final goal to facilitate pre-formulation studies, especially for those pharmaceutical technology laboratories that do not have access to the instrumentation necessary for a thorough investigation of silica materials structure (e.g., porosity and surface area measurements through the Brunauer, Elmer and Teller method (BET), and spectroscopic tools such as Fourier transform infrared (FTIR) and silicon-nuclear magnetic resonance (Si-NMR) analysis).

2. Experimental

2.1. General procedure for wet gel/xerogel preparation

Gels were synthesized by a two-step catalyzing method according to a procedure previously described [18]. An initial acid reflux "hydrolysis" step was followed by room-temperature catalyst-induced polymerization which was initiated together with the addition of the drug lidocaine (model compound) dissolved in ethanol, which was added to a final concentration of 2.5 mol/Si mol. Three types of formulations were obtained. Gel T was purely inorganic and was obtained from tetraethoxysilane (TEOS) only; gels M-A and M-B were obtained from a mixture of monomethyl-triethoxysilane (MTES):TEOS at a molar ratio of 20:80, using two distinct methods: in M-A preparation, MTES was added to the acid-hydrolyzed TEOS sol, whereas in M-B, MTES and TEOS were acid hydrolyzed simultaneously. The two procedures lead to matrices with different internal structures and retention properties (Fig. 1) [18]. In M-B, the methyl residues are homogeneously distributed within the matrix, whereas in the M-A formulation the methyl residues cluster outside the silica oligomers formed during the pre-hydrolysis step.

All gels were cast at room temperature by mixing the initial pre-hydrolyzed sols with the drug lidocaine (dissolved in ethanol), catalyst-containing water (final H_2O/Si = 4 and [Si] = 1.37 M) and, in the case of the M-A preparations, non-hydrolyzed MTES. After 3 days of wet aging at room temperature in closed vials under air, formulations were dried at 50 °C until constant weight was reached (~24 h). Xerogels were then ground and sieved using Endecotts sieves with openings from 600 to 63 μm. The sieved microparticles (600–500, 500–300 and 300–63 μm) were then remixed together at defined relative weight ratios (20:40:40) in order to obtain a homogeneous population of granules to be used in the release experiments (average diameter ~340 μm) [18]. They were then maintained in a desiccator at room temperature.

2.2. Characterization of the formulations

2.2.1. Gel time as a function of catalyst type and concentration

Several small gels (1 ml) were prepared in polypropylene tubes according to the general procedure described above. For each formulation type, three series of samples were prepared, one for each catalyst, and for each series several catalyst solutions at different concentration were used, so that their final content in the polymerizing sol varied between 0.1 and 3 % cat mol/Si mol (from 1.4 to 41 mM). After mixing, sols were sealed and the time of gel formation was recorded. Gel time is defined as the moment when the sol becomes semi-solid and cannot be further deformed upon inversion.

2.2.2. Syneresis of the wet form

This parameter was investigated on the purely inorganic T formulation only. Polymerization was carried as described above. After gel formation, samples were sealed and kept at room temperature. For each formulation, several small-scale (5 ml) wet samples were prepared, differing in catalyst type and concentration. At scheduled times, for up to 21 days, the liquid expelled as a consequence of the syneresis process was removed and quantified. Each individual formulation was prepared in two replicas, two for each time-point analyzed. The degree of syneresis was calculated as the ratio between the amount of solvent expelled and the initial sol volume prior to gelation (vol.%). This parameter was investigated within a range of catalyst concentrations of 0.045–1.25 % cat mol/Si mol (0.6–17.1 mM).

2.2.3. Drug release

Drug release was followed at 37 °C using a dissolution apparatus calibrated as recommended by laboratory good manufacturing procedures. Gel granules corresponding to 100 mg of drug were added to 600 ml of 10 mM Tris, 150 mM NaCl, pH 7.4. At scheduled times, 2 ml was removed for drug quantification and replaced with fresh buffer. Lidocaine concentration was determined by UV spectrophotometry at 263 nm according to a calibration curve, whereas silica content was measured by formation of the silica–molybdic complex [20]. Release data were fitted according to the Higuchi model [21]. The model allows the $D \times C_s$ value to be to obtained (D = drug diffusion coefficient through the matrix; C_s = drug saturation concentration in the matrix), which, in turn, is used to estimate the time needed for total matrix exhaustion (t_{ex}). Twenty-one matrices were tested as each of the three formulations (M-A, M-B and T) was analyzed at two concentrations for each of the three catalysts and compared with catalyst-free samples. All release experiments were carried out in duplicate.

2.2.4. Xerogel stability

Release experiments were carried out the day immediately after xerogel preparation (day 1) and 45 days later (day 45), upon storage of the dry gel at room temperature in a closed vial. Xerogel

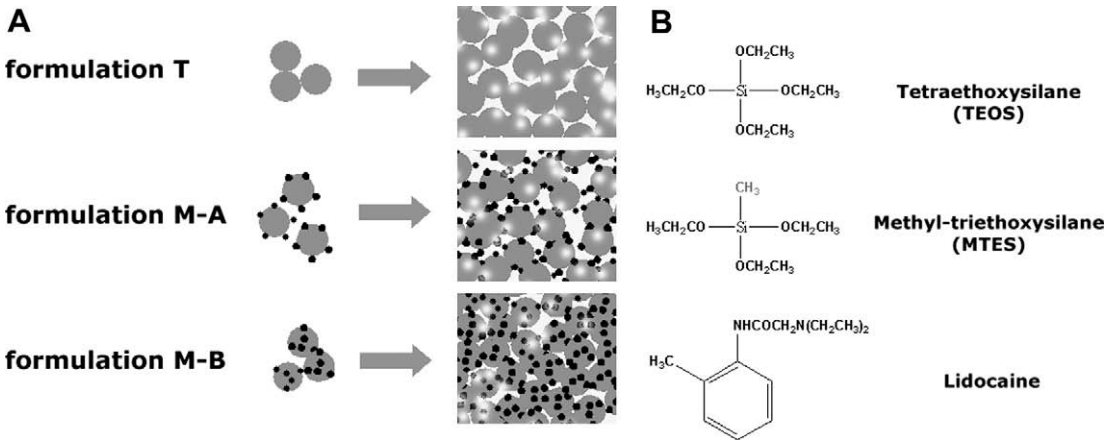

Fig. 1. (A) Schematic representation of formulation T, M-A and M-B initial polymerization clusters and final gel networks. The silica clusters are depicted in gray, the methyl residues in black. The remaining white areas in the figures indicate inter-particle spaces containing drug, catalyst and solvent. In M-A, the methyl residues are located at the periphery of the silica clusters. In M-B the methyl residues are located both at the periphery and internally to the cluster. (B) Chemical structure of TEOS, MTES and of the model drug lidocaine.

stability was estimated on the basis of the similarity factor (f_2), according to the FDA and European Medicines Evaluation Agency (EMEA) recommendations for in vitro equivalence of solid release dosage forms. The f_2 factor was calculated for each formulation by comparing its release profiles at day 1 and day 45, on the basis of the formula below:

$$f_2 = 50 * \mathrm{Log}\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}[\bar{R}(t)-\bar{T}(t)]^2}{n}}}\right]$$

where f_2 is the similarity factor, n is the number of time points, $\bar{R}(t)$ is the mean per cent drug released from the formulation at day 1, and $\bar{T}(t)$ is the mean per cent drug released from the same formulation at day 45. The release data were compared only below the maximum of 85% drug released, according to the official FDA and EMEA recommendations. The value of 50 for the f_2 factor represents the limit below which the two release profiles cannot be defined as "similar". In contrast, an f_2 value between 50 and 100 suggests that the two release profiles are similar: the higher the value, the greater the degree of similarity [22]. In the experimental set-up, formulations displaying a value of $f_2 \geqslant 50$ can be considered "stable". All release experiments were carried out in duplicate, and the f_2 value was calculated by comparing the trend of the averaged curves. No standard deviation was calculated.

3. Results

3.1. Gel time and wet polymer syneresis

Gel time varied between 1200 and 0.7 min, depending on the formulation, the catalyst type and the concentration. In the conditions tested, the presence of lidocaine (which, when alone, slightly accelerates polymerization [18]) was without influence, as gel time was the same independent of the presence or absence of the drug. In the case of formulation T, a logarithmic decrease in gel time as a function of catalyst concentration was observed with all compounds (Fig. 2) and, in the case of NaF and carbonate only, a minimum was reached (25 and 7 min at 0.6% and 1% cat mol/Si mol. Si/Si, respectively, corresponding to ~8.5 and 13.7 mM), above which no further reduction in gel time was observed. In contrast, no minimum gel time was observed in the case of the ammonia catalyzed process, at least within the concentrations investigated. The shortest gel time registered for NH_4OH was 0.7 min at 3 % cat mol/Si mol concentration (41 mM). Above this concentration, polymerization leads to opaque and a non-homogeneous gels, most likely due to the presence of solid SiO_2. Also gels obtained with Na_2CO_3 >0.8% cat mol/Si mol were opaque, in this case because above that concentration the catalyst is not fully soluble in the ethanol environment. No phase separation was observed with NaF at any of the concentrations tested.

Similar trends with ammonia and NaF were observed for M-A and M-B formulations. In fact, with ammonia no minimum was reached, while with NaF two minima were reached, namely 35 min for M-A and 110 min for M-B, at 2% and 1.25% cat mol/Si mol, respectively, corresponding to ~37.4 and 60 mM). In the case of Na_2CO_3, a plateau was reached with M-B but not with M-A, even if at high catalyst concentrations the differences in gel time between samples were minimal (even if statistically different).

The investigation on syneresis was carried out with the main purpose of searching for some correlation between wet gel parameters and xerogel stability. Owing to the large number of samples to be tested, this parameter was investigated on formulation T only. The evolution in time of the syneresis process of this formulation as a function of catalyst concentration is summarized in Fig. 3. The information for the different catalysts is represented separately in the right-hand panels, where the degree of syneresis is plotted as a function of catalyst concentration. The different curves in each panel refer to the data measured at different time points (up to 21 days) during wet-gel evolution. In the left-hand panels, the phenomenon time evolution at the catalyst concentrations selected for the release assays is represented.

The range of catalyst concentrations was more limited than that used for the gel time analysis (namely up to 0.8% for Na_2CO_3 and 1.25% for NH_4OH and NaF). In fact, as observed during the gel time experiments, concentrations of Na_2CO_3 >0.8% lead to catalyst separation, while NaF amounts >1.25% are likely to lead to toxic—and therefore useless—matrices (see Section 4). NH_4OH amounts were tested in the same range for comparative reasons.

The syneresis phenomenon tends towards an end-point which is reached at the latest time points independently of the concentration used. Na_2CO_3 and NH_4OH catalyzed samples reached a similar maximal syneresis value (33% v/v), while the NaF catalyzed samples showed a significant lower gel contraction (25–30% v/v). In the early phase of aging (days 1 and 3), the degree of syneresis is highly influenced by the amount of catalyst, but the dose–effect

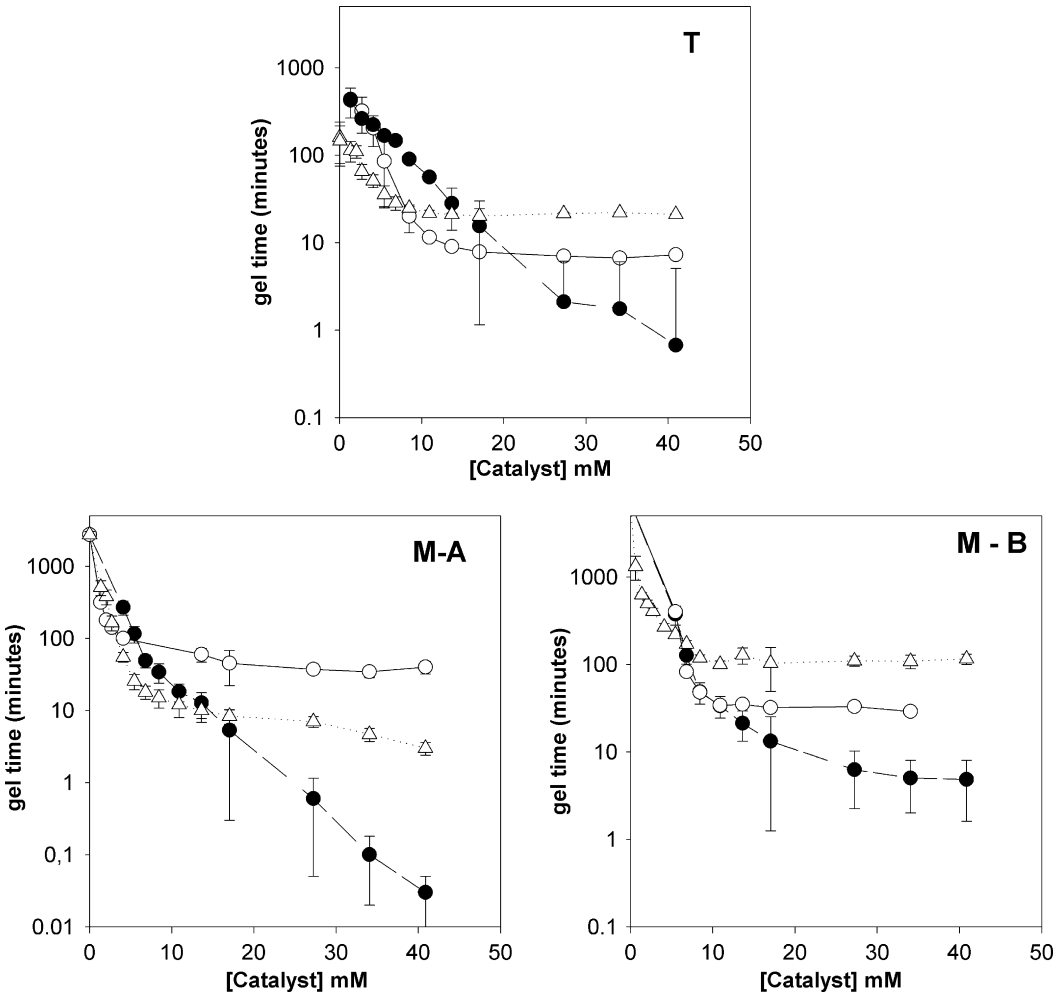

Fig. 2. Gel time for formulations T, M-A and M-B of as a function of catalyst type and concentration: ●, NH_4OH; ○, Na_2CO_3; △, NaF. Errors indicate the standard deviation ($N = 4$).

flattens between days 3 and 7. Based on this observation, a time of 3 days was selected for aging those formulations that were tested for release and stability. The concentration dependence in the early phase is more evident for Na_2CO_3 and NH_4OH gels for which a positive correlation between catalyst concentration and syneresis exists up to 0.6% (8.8 mM) for carbonate and 1.25% (17 mM) for ammonia. In contrast, in the case of fluoride, a positive correlation is observed at the lowest catalyst concentrations only, whereas a small but significant inverse correlation between syneresis and catalyst concentration was observed at catalyst concentrations >0.1 % cat mol/Si mol ($[F^-] = 1.37$ mM). As to the kinetics of the phenomenon, a linear evolution with the logarithm of time is observed (not shown).

3.2. Drug release and xerogel stability

Twenty-one xerogels where tested, namely M-A, M-B and T formulations, obtained either without catalyst or with each of the three catalyst investigated at three concentrations which were selected (Table 1) on the basis of the following rationale (a) at least one concentration had to be the same for all compounds tested (to allow a direct dose/effect comparison); (b) the lowest concentration of each catalyst was one among those below the plateau observed in the gel time plot; (c) the highest concentration had to lead to at least 85% of the final syneresis volume at day 3 (the day at which drying was performed for all samples).

3.2.1. Release properties

Fig. 4 shows the release profiles observed for all xerogels obtained either without catalyst or in the presence of NH_4OH, Na_2CO_3 and NaF at the highest concentrations investigated. In this figure, the release measured both the day after preparation and after 45 day's storage is displayed to appreciate xerogel (in)stability. Each release assay was carried out in duplicate. Table 2 summarizes all release data expressed in the form of t_{ex} (time to matrix exhaustion) values.

Xerogel release behavior changes with the type and concentration of catalyst used. This is clear when comparing the release profiles registered from xerogels after 45 days of storage, a time considered enough to stabilize even an "unstable" gel [18].

Analysis of T xerogels obtained with NH_4OH or NaF shows that they release the drug faster than the catalyst-free formulation, and the effect of both catalysts is dose-dependent (Table 2). In contrast, Na_2CO_3 leads to more retentive formulations and has no impact on the end-point release of the purely inorganic xerogel: t_{ex} at day 45 is similar (50–60 h) for catalyst-free and Na_2CO_3-containing samples. As to the two organically "doped" formulations, all catalysts accelerate the release rate in a dose-dependent manner, but the effect is more pronounced with NH_4OH and NaF, and less with carbonate, especially in the case of the M-A gels.

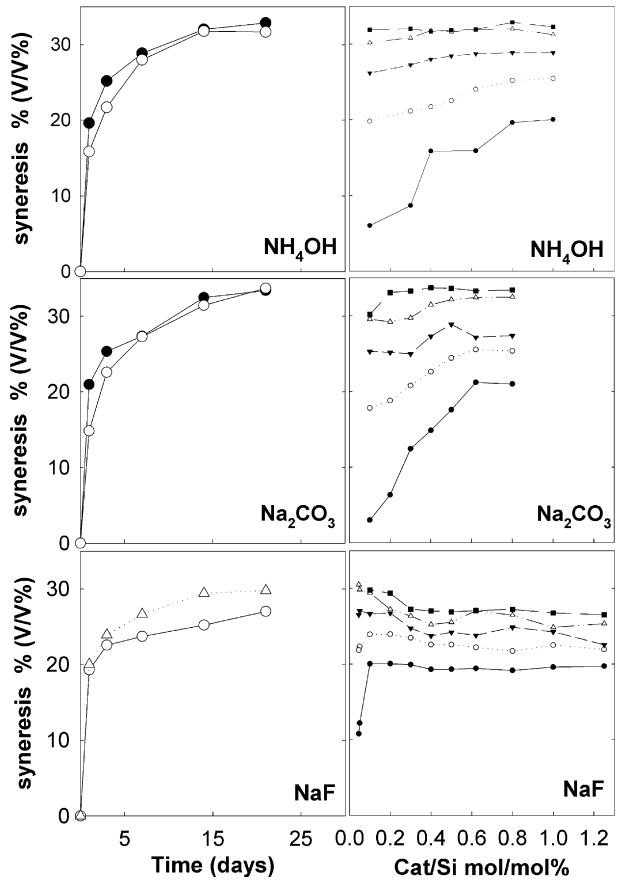

Fig. 3. Time evolution of formulation T wet syneresis as a function of catalyst type and concentration. The degree of syneresis (vol.%) was calculated as the % ratio between the volume of the solvent expelled along the process and the one of the gels immediately after formation. Left-hand panels: syneresis time evolution at the catalyst concentrations selected for the release assays: △, 0.1%; ○, 0.4%; ●, 0.8% cat mol/Si mol; right-hand panels: syneresis value as a function of catalyst concentration at each day of analysis: ●, day 1; ○, day 3; ▼, day 7; △, day 14; ■, day 21; the data are the average of three experiments.

Table 1
Type and amounts of catalysts selected for the preparation of formulations assayed in release and stability experiments.

Type of catalyst	Concentrations tested (% cat mol/Si mol)
NaF	0.1 and 0.4
Na_2CO_3	0.4 and 0.8
NH_4OH	0.4 and 0.8

The stability data are summarized in Table 3. Stability was determined by measuring the f_2 value, which measures the similarity of the release profile of lidocaine. The f_2 value for each formulation was calculated by comparing its release at day 1 with that on day 45 after preparation. Stable T xerogels were obtained with Na_2CO_3 at all concentrations, and NaF at the higher concentrations only. T xerogel stability was also improved in a dose-dependent manner by the use of NH_4OH, but this catalyst failed to produce formulations that were totally stable. NH_4OH failed to stabilize M-A and M-B gels. Interestingly, Na_2CO_3, the best stabilizing catalyst identified with the inorganic T formulation was able to stabilize the M-B gel (at its highest concentration) but was inefficient with M-A, for which NaF proved to be the best stabilizer (again at the highest concentration considered). As a general observation, the effect of the catalysts on the release behavior appears unrelated to their stabilizing property.

4. Discussion

The ability to retain an embedded compound is a property of the xerogel which, in addition to chemical affinity between the embedded compound and the matrix, is secondary to the internal structure of the latter. Consequently, the release behavior of a drug-embedded xerogel reflects in part its network properties, whereas changes in this parameter upon storage are indicators of its (in)stability.

Sol–gel materials are capable of assuming several nano- and micro-scale morphologies by varying synthesis and processing conditions [1,7,10,13,17,18,23]. The release of an embedded compound occurring by diffusion and/or dissolution is dependent on the surface area of the gels, the pore volume and the silicon condensation rate [3,7,10,18,24–26]. The method of preparation influences the polymer network in its final conformation as well as along several phases during its formation. The properties of the polymer keep changing for a long time after the macroscopically evident gel formation, and this tendency to evolve leads to potential instability. Since stabilization by high temperature curing cannot be done when sol–gel materials are polymerized in the presence of bioactive organic compounds, alternative means of stabilization must be found, especially for those applications (as in the case of slow release formulations) where stability and reproducibility are fundamental requirements.

The effects induced by three compounds known to be capable of catalyzing hydrolysis and/or condensation reactions thanks to either their basic behavior (ammonia and carbonate) or their ability to interact directly with the silicon center (fluoride) were investigated here. More precisely, ammonia and sodium carbonate were selected because a mildly basic environment accelerates sol–gel hydrolysis and condensation reactions. NaF was selected because of its pH-independent catalytic effect on silicon reactivity [27–29].

It must be pointed out that the selection of a catalyst dedicated to the synthesis of matrices for pharmaceutical purposes should take into account not only chemical issues but also toxicity matters. The three compounds here investigated and the concentrations at which they were tested were selected also taking into account toxicity issues. While carbonate is a non-toxic compound, both ammonia and fluoride are potentially harmful if used above certain levels. However, since ammonia is removed upon heating, even at mild temperatures, toxicity matters do not really apply in this case. In contrast, NaF concentration cannot be increased indiscriminately. The amounts used here are such that the highest concentration tested would lead to xerogels whose *F*-content/gram does not exceed the maximum daily intake (3–4 mg) recommended for cavity prevention by the Food and Nutrition Board of the US Institute of Medicine [30]. This amount of fluoride would not be expected to represent a risk even in the case of frequent repeated administration, as could be the case of an oral use.

The data show that all three catalysts affect (a) gel time, (b) release and (c) stability, but each displays unique properties.

It was reasoned that differences in the release profiles are likely to reflect different structural properties of the polymer internal network, whereas the differences observed in stability must be related to the different residual reactivity of the pore surface silanols [19]. With respect to the network porosity, ammonia and fluoride are known to increase the porosity of sol–gel silica [23,28,31,32], whereas information regarding the effect of the carbonate has, to the authors' knowledge, not yet been described. As a matter of fact, both ammonia and Na_2CO_3 are bases, and their catalytic effect should be mediated by the same catalytic mechanism on hydrolysis and condensation reactions. If this were the case, they would be observed for a similar effect on both retention and stability properties. Therefore, the fact that the two catalysts display different behavior is difficult to explain in terms of their impact on reaction

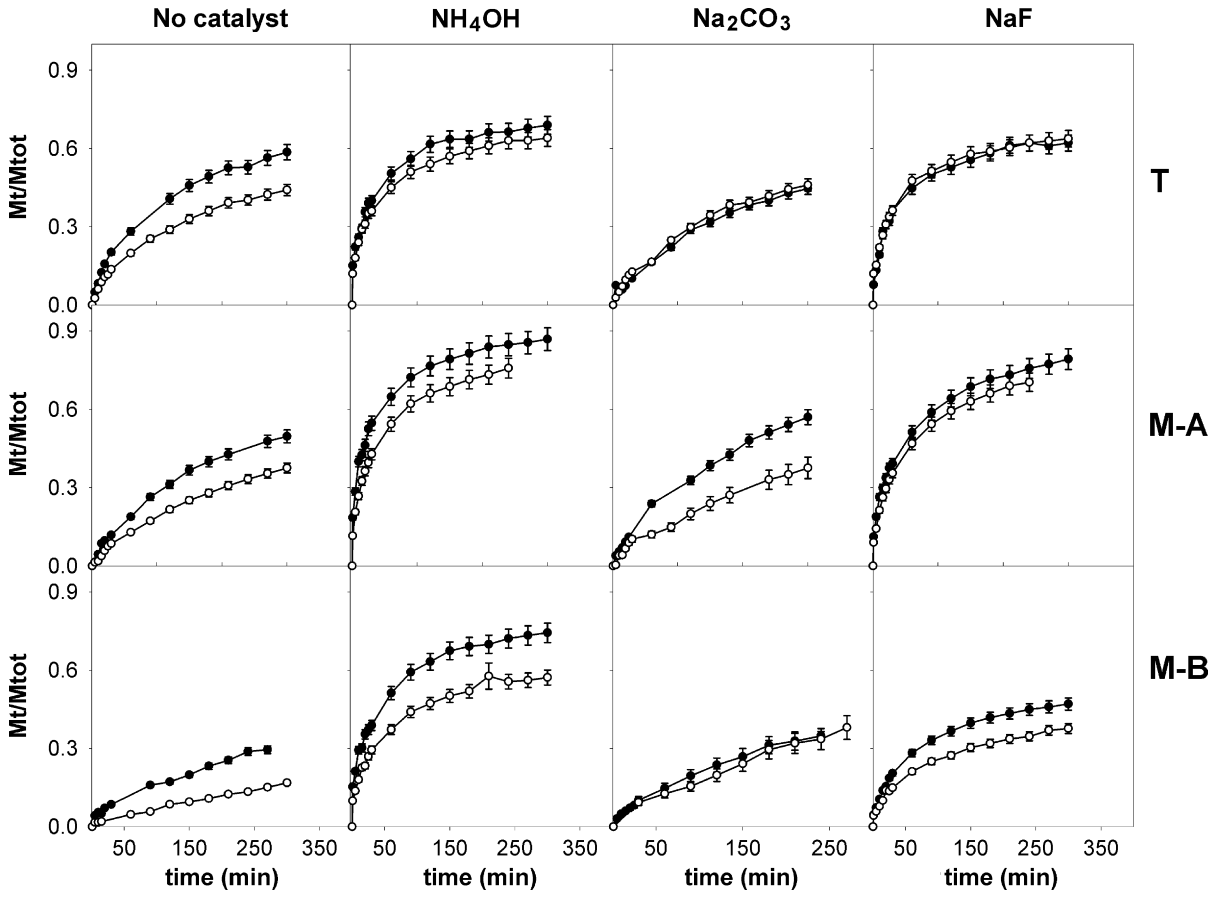

Fig. 4. Release profiles observed from T, M-A and M-B xerogels obtained without catalyst, or in the presence of NH_4OH, Na_2CO_3 and NaF at the highest concentrations investigated. Release data were recorded at day 1 (full symbol) and day 45 (empty symbol) after xerogel preparation. Data are expressed as M_t/M_{tot}, where M_t is the amount of drug release at time t, and M_{tot} is the total drug embedded in the xerogel. Errors indicate the standard deviation ($N = 3$).

Table 2
Time to matrix exhaustion, as measured for all matrices the day after preparation and after 45 days of storage; errors indicate the standard deviation ($N = 3$).

Formulation	No catalyst	NH_4OH		NaF		Na_2CO_3	
		0.4%	0.8%	0.4%	0.8%	0.4%	0.8%
Time to matrix exhaustion (days) d1 → d45[a]							
T	22.5 ± 0.6 → 56 ± 1.1	20 ± 3 → 30 ± 12	7 ± 2.2 → 10 ± 2.2	23 ± 0.2 → 32 ± 12.7	19 ± 2.2 → 17 ± 2.4	62 ± 2 → 57 ± 1.2	57 ± 1.6 → 52 ± 2
M-A	32 ± 1.6 → 76 ± 4.1	10 ± 1.7 → 13 ± 4.4	7 ± 1 → 10 ± 1	11 ± 1.5 → 13 ± 0.9	10 ± 0.8 → 13 ± 0.7	21 ± 0.4 → 32 ± 2	28 ± 1.5 → 63 ± 5.4
M-B	138 ± 7 → 524 ± 46.4	33 ± 0.5 → 66 ± 3	11 ± 1.3 → 22 ± 2.2	50 ± 2 → 153 ± 3	37 ± 2.3 → 70 ± 3	47 ± 3 → 108 ± 7	80 ± 3.7 → 61 ± 12.4

[a]Formulations shaded in gray display an f_2 factor >50.

rates [33]. It is therefore hypothesized that the unique effect of carbonate could be due to its chemical interaction with the silicon center, secondary to which the carbonate moiety becomes directly involved in the polymeric network and acts as a bridging unit between two silicon atoms (–Si–O–CO–O–Si–). If this were the case, a more compact structure would form, explaining why the Na_2CO_3 catalyzed samples are generally the most retentive ones. This is the case for all three types of xerogels, even if interpretation of the release data obtained with the two organically "doped" formulations M-A and M-B is complicated by the inductive, steric and hydrophobic effects induced by the methyl residue [7,18,34]. Despite the fact that both formulations are obtained using the same ratio of the TEOS:MTES precursors (80:20), the different synthetic procedures employed lead to different spatial distributions of the methyl groups within the polymer matrix (Fig. 1) [18] and, in the absence of a catalyst, this causes major differences in gel time and syneresis time evolution, the latter being also responsible for the wet gel mechanical resistance build-up. In fact, the methyl group also acts as a poison for the condensation (i.e., blocks one condensation site on the silicon), and this results in a more open network, which also exhibits more flexibility and can result in denser xerogels. In particular, the catalyst-free M-B formulation (even if containing the slightly basic lidocaine, which, alone, promotes polymerization) evolves so slowly that the 3 day's aging employed in the experiments do not allow the wet gel to reach enough mechanical resistance to enable it to resist the compression forces developed during solvent evaporation. The resulting xerogel becomes very compact, and releases the drug slowly. When any of the catalyst was added to this formulation, gel formation, syneresis and mechanical resistance build-up were accelerated, and the resulting xerogel released the drug much faster, most likely because a more porous structure was obtained. In contrast, lidocaine containing M-A polymerizes more quickly, and the 3 day's aging are enough to build-up sufficient mechanical resistance and lead to the porous structure even in the absence of a catalyst. In this case, the effect of the catalyst on the drug-releasing properties is

Table 3
Release samples similarity factors (f_2) estimated according to FDA and EMEA recommendations (see text)[a].

% Catalyst (% cat mol/Si mol)	f_2		
	M-B	M-A	T
No catalyst	49	44.8	40.2
	NH_4OH		
0.4	54.6	56.5	49.8
0.8	45.8	49	56.2
	Na_2CO_3		
0.4	54.4	53.6	83.7
0.8	78.6	49.5	80.9
	NaF		
0.1	49.2	61.6	71.2
0.4	57.7	66.8	83

The release experiments were carried out in duplicate, and the f_2 value was calculated by comparing the trend of the averaged curves. No standard deviation was calculated.

[a] The similarity factors, calculated comparing the release of profile of individual formulations at day 1 and day 45 after their preparation, were used to estimate samples stability. According to the official Pharmacopeia, two formulations displaying a similarity factor $\geqslant 50$ are considered "similar". Therefore, in the present case, a formulation displaying a f_2 value $\geqslant 50$ can be considered "stable".

similar to that observed with formulation T: ammonia and fluoride accelerate release, whereas Na_2CO_3 slows it down.

As far as stability is concerned, stable T xerogels were obtained using both fluoride and carbonate, whereas ammonia failed to produce stable formulations at all concentrations tested. It was assumed that the stability of a xerogel is related to the residual reactivity of surface silanols that remain available for condensation reactions after drying [19]. Therefore, the differences observed between the three catalysts are probably due to their different ability to favor condensation over hydrolysis, which could be the case for carbonate and fluoride but not for ammonia. However, the strong stabilizing property of Na_2CO_3 might be also explained through the silica-carbonate bridging hypothesis already discussed with the release data. This theory could also explain why Na_2CO_3, was able to stabilize the M-B gel, but was inefficient with M-A, at least at the catalyst concentrations tested, where the spatial distribution of the methyl residues (Fig. 1) probably impairs the formation of the stabilizing carbonate bridges between the initial gel clusters. In contrast, the methyl residues in M-B gels are not locally clustered but are more homogeneously distributed (Fig. 1) so that the carbonate still has the possibility to bridge.

As far as sodium fluoride is concerned, stable T and M-A formulations were obtained with all concentrations tested, with f_2 values higher for T than for M-A gels. In the case of M-A, NaF proved to be the best stabilizer of all. However, NaF was less efficient than Na_2CO_3 with the intrinsically more unstable M-B gel, where stable formulations were obtained at high catalyst concentrations only and with lower f_2 values than in the carbonate catalyzed samples. This catalyst probably acts in a similar way to ammonia but, compared with this compound, it is more efficient in promoting condensation reactions. This difference could be due to steric reasons related to the spatial distribution of the methyl groups deep within the initial polymerization clusters, which in the case of M-B prevent efficient catalyst penetration.

The second purpose of this work was to identify one or more data deriving from the wet gel synthesis process that could act as stability predictors before the drying step is carried out. This could facilitate pre-formulation studies and be of help, especially for those laboratories that are in the process of carrying out pre-formulation studies and do not have access to the classical instrumentation used to characterize the inner structure of sol–gel materials. The authors therefore tried to correlate the stability data with the gel processing parameters, namely gel time and wet syneresis time evolution. Stable xerogels were obtained using both carbonate and fluoride but not ammonia. Thus at the same time similarities between NaF and carbonate catalyzed samples and dissimilarities with ammonia catalyzed ones were sought, within parameters related to gel time and syneresis. Unfortunately, the data did not provide strong evidence for the existence of a stability predictor parameter (a) gel time alone cannot be used, as all the compounds are very efficient at shortening the process of gel formation; (b) on analysis of the trend of syneresis, ammonia and carbonate show similar behavior which, however, is very different from that displayed by fluoride: again, this parameter cannot be used to predict stabilizing efficacy; (c) the only possible correlation comes from the trends of gel time vs. catalyst concentration, where the two stabilizing catalysts, carbonate and fluoride, but not ammonia, showed a plateau. The presence of a plateau in gel time vs. catalyst concentration could therefore be a potential predictor of stability. Nevertheless, more data are necessary to provide sound evidence for this hypothesis, and further experimentation is necessary before a final conclusion is reached.

5. Conclusions

To the authors' knowledge, this is the first time that chemical catalysts have been specifically investigated as potential stabilizers in sol–gel processed silica. Overall, the results show that fluoride and carbonate, but not ammonia, are efficient stabilizers of low-temperature processed xerogels. Both compounds are capable of stabilizing, in a dose-dependent manner, purely SiO_2 xerogels, whereas, in the case of the hybrid organic–inorganic formulations, they somehow display complementary activity. However, it is important to note that fluoride is toxic above certain levels, and this may limit its use in some cases.

The results also show that the trend of gel time vs. catalyst concentration might be a potential parameter to monitor when searching for a stability-promoting catalyst. This result is still qualitative, and further spectroscopic investigation (NMR, FTIR, BET) should be carried out to confirm this observation and also to correlate the stability data with structural information. Nevertheless, detailed structural information is beyond the scope of this work, and the data shown here may still be of practical interest not only for the field of drug release, but also in the several and continuously expanding areas of application of the sol–gel technology.

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