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Multi-component supramolecular gels for the controlled crystallization of drugs: Synergistic and antagonistic effects

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The applicability of multi-component gels, based on the combination of Lys-based dendrons and alkyl amines, for the crystallization of common drugs is presented. The results presented herein demonstrate that active pharmaceutical ingredients (APIs) with no carboxylic acid in their structure readily crystallize inside the organogels formed by a second generation lysine-based dendron (G2-Lys) and aliphatic amines. The thermodynamic parameters (ΔH_{diss}, ΔS_{diss} and ΔG_{diss}) of the corresponding three-component mixture (API+G2-Lys dendron + amine) have been calculated by using VT ^{1}H NMR. Interestingly, the presence of carbamazepine (CBZ) in the mixture of G2-Lys and decylamine allows efficient gelation at room temperature in contrast with the behaviour observed for an unmodified G2-Lys dendron and decylamine mixture that only forms toluene gels at -20ºC – a synergistic effect in which the API enhances gelation. On the other hand, aspirin (ASP) or indomethicin (IND), that possess a carboxylic acid in their structure, do not crystallize inside the organogel formed by G2-Lys dendron and the amine – indeed they prevent formation of the gel. The K_a values of the complexes G2-Lys···decylamine and IND···decylamine have been calculated by ^{1}H NMR titrations in toluene-d8. The higher K_a value for the complex IND···decylamine justifies that this pair is thermodynamically favoured thus preventing the formation of the complex between the Lys-based dendron and the amine, which underpins gel fibre assembly, and also preventing effective crystallization of the API –an antagonistic effect. Overall, these results demonstrate the active roles played by all components when multi-component gels are used for API crystallisation.

Introduction

Gels are attractive examples of soft matter present in many aspects of our daily life such as cosmetics, food or biomaterials.[1] Despite the large number of reports dealing with polymer-based gels,[2] the supramolecular variant of gels, named low-molecular weight gels (LMWGs) or supramolecular gels are being actively investigated since they have found application in research and technology fields just as varied as those described for polymeric gels.[3] In these LMWGs, the self-assembly of suitable organic molecules by the operation of non-covalent forces results in the formation of fibrillar structures that are further intertwined to yield a complex sample-spanning network capable of supporting the solvent.[3]

An intriguing variant of supramolecular gels is constituted by multi-component systems. In multicomponent gels, two or more species, interacting by non-covalent forces, form suitable building blocks that are able to interact to yield the fibrillar network which underpins the gel.[4] The incorporation of different functional groups in multicomponent gels can bias the applicability of the gel. Of special interest is the orthogonality, or selective assembly, achieved in multicomponent gels that allows the morphology of the formed aggregates to be switched,[5] as well as the self-sorting effects that can be observed in multicomponent gels that give rise to independent fibre networks with orthogonal functions.[6] More relevant is the component selection exhibited by multicomponent gels that allows the incorporation and immobilization of certain substances ignoring others that remain in solution.[7] LMWGs are being utilized as crystallization media for different substances.[8] Importantly, the interest of pharmaceutical industry in new and effective ways of drug formulation is currently prompting the use of both conventional or supramolecular gels as media for controlling the crystal growth of different polymorphs of drugs.[9,10] The physical encapsulation of active pharmaceutical ingredients (APIs) inside

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supramolecular gels can itself be considered as an example of a multicomponent gel[11a] in which the API may establish non-covalent interactions with the gelator.[11b] However, to the best of our knowledge, the utilization of multi-component supramolecular gels as crystallization media and the potential influence of the presence of APIs on the formation or on the disruption of the complexation process which underpins the gelation process in such multi-component systems has not previously been explored.

The results presented herein shed light on the applicability of two-component gels as crystal growth media for APIs, report and define both synergistic and antagonistic multi-component effects, both on gel assembly and API crystallisation, and suggest ground rules as to which APIs can be successfully crystallized inside these two-component gels.

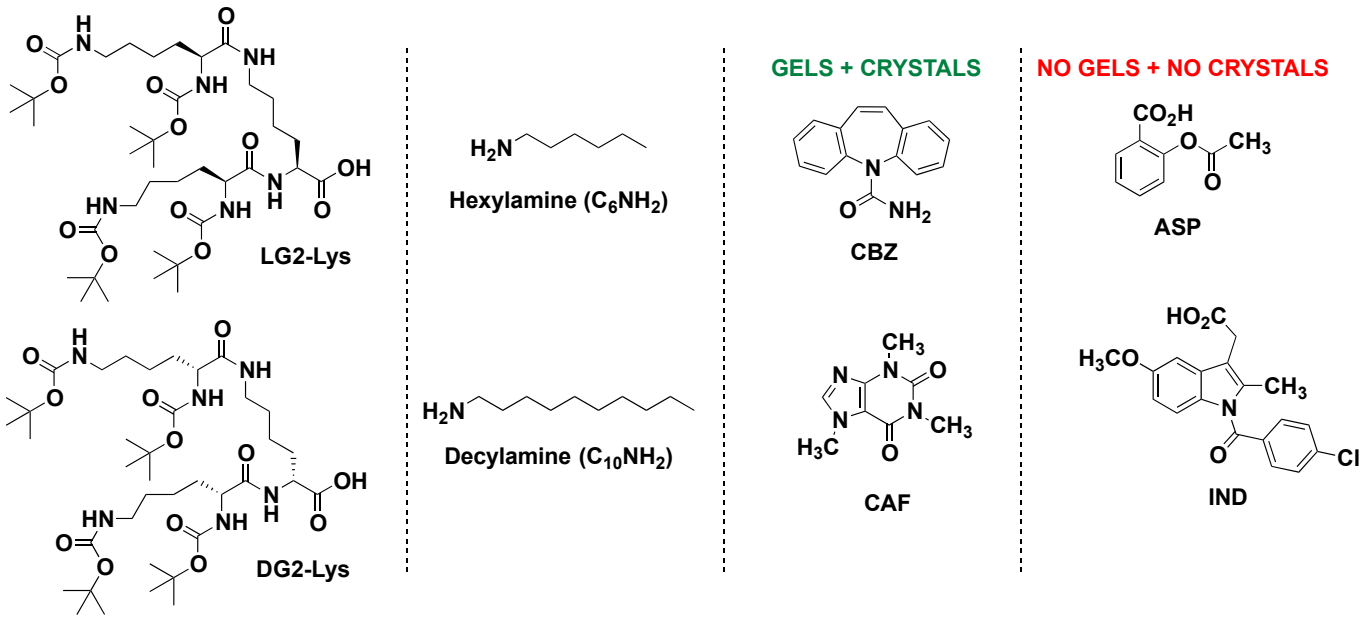

Fig 1. Two-component gelation system comprising *L*G2-Lys or *L*G2-Lys and a primary monoamine. The chemical structure of the APIs used and the final results regarding gelation and crystallization are indicated in the right-part of the panel.

Materials and methods.

Synthesis. Both *L*G2-Lys and *D*G2-Lys were prepared by following the synthetic methodology previously reported for these aminoacid derivatives.[7,20]

Preparation of the gels. Stock solutions of the G2-Lys dendron and the corresponding amine were prepared. Amounts of these solutions were mixed together in a 2 mL vial with any excess of toluene if required. The resulting mixture was then heated to the boiling point of the solvent. This solution was then left to cool at room temperature (25ºC) until the gel formed. To check the formation of the gel a simple inversion of the vial was used.

Crystallization of the APIs inside gels and characterization of the crystals. The preparation of the samples to demonstrate the ability of the reported gels to act as crystal growth media is similar to that described for the preparation of the gel with the only difference being that the corresponding API is added to the vial together with the mixture of the Lys-based dendron and the corresponding amine at a concentration of 1% wt/vol. The mixture was heated to the boiling point of the solvent until all three components were completely dissolved. After that, the mixture was allowed to reach 25ºC. The characterization of the crystals was performed by using X-ray diffraction in a Panalytical X'Pert PRO diffractometer with Cu tube and primary beam monochromator (lambda $K\alpha_1$=1.5406 Å) operated at 45 kV, 40 mA, programmable divergence slit working in fixed mode, and fast linear detector (X'Celerator) working in scanning mode. Samples, including gel and API crystals, were deposited on "zero background" silicon sample holders and measured in reflection geometry. To prevent solvent evaporation in gel samples, the sample holders were enclosed in a cell with an x-ray window covered by kapton foil. The obtained diffractograms show the crystalized API peaks on top of a bulged background resulting from the contribution of both the gel and the kapton foil, but still useful for polymorph screening.

Titration experiments. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. The solution of the corresponding substrate (decylamine or IND) in toluene-d8 at 2 mM and at 298 K was titrated by adding known aliquots of concentrated solutions (60 mM) of the corresponding ligand (*L*G2-Lys dendron or decylamine). The guest solutions used to effect the titration contained the substrates at the same concentration as the substrate solution into which they were being titrated so as to obviate the need to account for dilution effects during the titrations.

Results and discussion

Crystallization inside two-component gels. *N*-Boc-protected Lys-based dendrons have been reported to efficiently interact with primary amines by the formation of an acid-base complex between the free carboxylic acid of the dendron and the $-NH_2$ group of the amine. In organic solvents like toluene, the resulting H-bonded

complex is then able to hierarchically interact to form one-dimensional fibres through intermolecular amide-amide hydrogen bond interactions between peptide dendrons. These fibres then intertwine and finally yield a stable gel. The side chain of the primary amine plays a relevant role in the gelation features of the two-component system. Thus, 10 mM solutions of both dendron and hexylamine in toluene spontaneously form a gel that it is completely dissolved by heating. After leaving the mixture to reach room temperature, a homogenous gel is then formed. This is not the case for decylamine, which upon combination with the G2-Lys dendron and heating does not form the gel at room temperature but rather only on cooling to -20ºC.[12]

Taking into account the reported precedents of supramolecular gels to act as crystal growth media for drugs,[10] we have checked the ability of the two-component gel formed from both the *L*- and *D*-LysG2 dendrons and hexylamine to crystallize CAF, CBZ, ASP and IND. All of these pharmaceutical ingredients have been reported to crystallize in toluene as solvent and all of them can form different polymorphs.[13-16] The current study allows us to evaluate for the first time the ability of two-component organogels to act as crystallization media for APIs and, at the same time, investigate the potential control of the polymorphism of the obtained crystals.

We first tested the organogel formed by the combination of *L*G2-Lys dendron and hexylamine at 10 mM in toluene. Prior to heating these two components, we added the corresponding API at a concentration of 1% wt/vol. The mixture of the three components was heated to the boiling point of the solvent and left to reach room temperature. In the case of ASP and IND, the incorporation of the API to the mixture of the Lys-based dendron and hexylamine resulted in the inhibition of gelation, and furthermore, no API crystallization was observed (Table 1) – an antagonistic effect. The presence in both ASP and IND of a carboxylic acid group and the subsequent competence to interact with the amine can reasonably justify these results. In the next section, we quantify this effect.

In the case of CAF and CBZ, the G2-Lys/hexylamine gel was readily formed, and furthermore, the crystals of these two drugs appeared in the next hours (Table 1 and Figure S1-S4). In the case of CAF, polymorph II was obtained in all mixtures as well as in pure toluene (Figure S1 and S2). The results on polymorphism of CBZ were slightly different, and in the case of the two-component gels, the mixture of polymorphs II and III was generally observed (Figure S3 and S4).

The morphology of the crystals of CBZ and also the organogel resulting from mixing the *L*G2-Lys dendron, hexylamine and CBZ, as representative examples of the three-component mixtures, have been visualized by scanning electron microscopy (SEM). Inside the organogels, it is possible to visualize two types of crystals, most probably due to the formation of polymorphs II and III of CBZ (Figure 2 and S5). Figure 2a clearly shows the presence of large prism-like structures together with thinner needle-like crystals. Covering some CBZ crystals, it is possible to see the twisting fibres constitutive of the organogel (Figure 2b and S6). These long fibres are bundled forming a dense network. The SEM images exhibit an average thickness of 40 nm. The morphology and dimensions of the fibres of the organogel are analogous to those reported previously for the *L*G2-Lys dendron-hexylamine organogel and some other multicomponent gels based on these motifs.[12, 17]

Table 1. Crystallization of APIs in the mixtures of the Lys-based dendrons and the monoamines. The polymorphs of the studied APIs formed in pure toluene are also reported for comparison purposes.

API[a]	*L*G2-Lys/C_6NH_2[b]	*D*G2-Lys/C_6NH_2[b]	*L*G2-Lys/$C_{10}NH_2$[c]	*D*G2-Lys/$C_{10}NH_2$[c]	Tol
ASP	—	—	—	—	I
IND	—	—	—	—	III (ß)
CBZ	II+III	II+III	III	II+III	III
CAF	II (ß)	II (ß)	II (ß)	II (ß)	II (ß)

[a] The concentration of API is of 1%wt/vol; [b]the concentration for both G2-Lys dendron and hexylamine is 10 mM; [c] the concentration for both G2-Lys dendron and decylamine is 20 mM. In brackets, the Greek notation of polymorphs II and III of CAF and IND, respectively, is included.

The combination of the G2-Lys dendrons with amines possessing longer alkyl chains has been reported to form a stable gel in toluene only on cooling to -20ºC.[12] Herein, we have demonstrated that the addition of APIs with no carboxylic acids, such as CAF or CBZ, enables the improved formation of these gels at room temperature – a synergistic effect – and it is therefore possible to utilize two-component toluene gels composed of these dendrons and decylamine as crystal growth media. The crystals obtained in these G2-Lys-dendron and decylamine gels were similar to those obtained in the gel formed from hexylamine. Thus, the polymorph II of CAF is detected (Table 1, Figure S7 and S8) whilst for CBZ, XRD analysis revealed the formation of the mixture of polymorphs II and III for the *D*G2-Lys dendron but only polymorph III for the *L*G2-Lys dendron (Table 1, Figure S9 and S10). In good analogy with that observed for hexylamine, the SEM images of the gel formed from *L*G2-Lys dendron and decylamine show the presence of the CBZ crystals together with a dense network of fibrillar structures that partially cover the crystals (Figure 2c).

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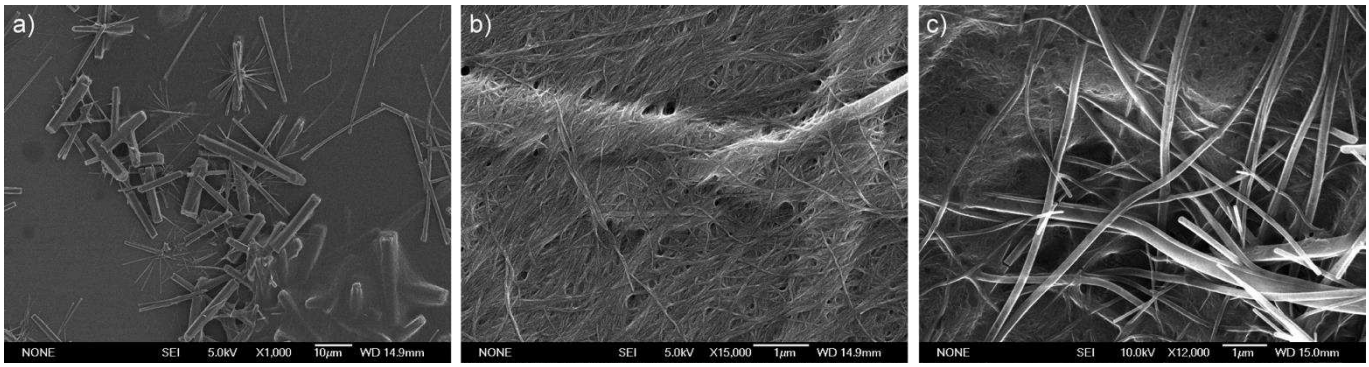

Fig 2. SEM images of (a) the two types of CBZ crystals obtained inside the multicomponent gel formed by the *L*G2-Lys dendron and hexylamine, and (b) the fibres constituting this *L*G2-Lys dendron-hexylamine organogel. (c) SEM image of the fibres constituting the *L*G2-Lys dendron-decylamine organogel and the CBZ crystals that crystallize inside this gel.

The SEM images of the organogel formed by *L*G2-Lys dendron and hexylamine utilized to crystallize CBZ demonstrate the negligible influence of the presence of API inside the organogel on the morphology of the fibrillar structures. However, an intriguing question is to quantify the influence of the presence of the API on the thermodynamic parameters associated with the stability of the gel and, consequently, with the non-covalent interactions responsible for the formation of the supramolecular entities that constitute the gel. Variable-temperature (VT) ^{1}H NMR experiments in toluene-d8 have been used to precisely derive the enthalpy (ΔH_{diss}) and entropy (ΔS_{diss}) associated with the gelation process.[18] A sample formed by a mixture of *L*G2-Lys dendron, hexylamine and CBZ at a concentration of 10 mM was slowly heated at intervals of 5ºC.[12] The use of diphenylmethane as internal standard allows quantification of the mobile material inside the NMR tube. Unlike the ^{1}H NMR spectrum of the two-component gel formed by *L*G2-Lys dendron and hexylamine at 10 mM in toluene-d8 and at 25ºC, the addition of CBZ results in the presence of a significant residual amount of dendron (Figure 3a) and unbound hexylamine (Figure S11) at this temperature. Increasing the temperature induces the disassembly of the organogel and the amount of the constitutive components of the gel increases (Figures 3a and S11). At 49ºC, the concentration of the components in solution reaches the maximum of 10 mM and does not increase any further on increasing the temperature further. This implies that the organogel is completely disassembled at this temperature, which is much lower than the 73ºC calculated for the disassembly of the two-component gel formed by the *L*G2-Lys dendron and hexylamine in the absence of API. This implies that the CBZ substantially lowers the thermal stability of the organogel.[12]

The VT-^{1}H NMR experiments also allow a derivation of the thermodynamic parameters associated with the gelation/dissolution process by applying a van't Hoff treatment of the measurements in the range of temperatures that provoke the solubilisation of the gel (Figure 3b). The calculated values of ΔH_{diss} and ΔS_{diss} for the mixture of CBZ, LG2-Lys dendron and hexylamine are 19.6 kJ/mol and 22.6 J/molK, respectively (Table 2). These values are much smaller than those calculated for the LG2-Lys dendron and hexylamine gel (ΔH_{diss} = 90.5 kJ/mol and ΔS_{diss} =226 J/molK) and are in good agreement with the observed dissolution temperatures.[12] The calculated values of ΔH_{diss} and ΔS_{diss} indicate that the gelation process is enthalpically favoured as a consequence of the operation of stronger interactions between the supramolecular entities, but entropically disfavoured due to the higher organization exhibited by the gel in comparison to the molecularly dissolved species. The lower values in the three-component system would indicate that CBZ, at least to some extent, lowers the degree of fibre organisation and the enthalpic gain of self-assembly, presumably as a result of the microscale crystals somewhat disrupting the overall growth of the nanoscale network. The balance between enthalpy and entropy results in a value of the Gibbs free energy (ΔG_{diss}) of -12.8 kJ/mol for the formation of the three-component gel.

The thermodynamic parameters associated with the gelation of the mixture of CBZ, *L*G2-Lys dendron and decylamine have also been calculated by using VT ^{1}H NMR experiments (Figures S12 and S13). Despite a critical temperature for disassembly of 45ºC for this three-component mixture (Figure S13a), the calculated values for ΔH_{diss} and ΔS_{diss} are 55.4 kJ/mol and 141.3 J/molK, respectively (Figure S13b). These thermodynamic parameters are intermediate between those obtained for the two-component mixture of *L*G2-Lys and hexylamine and the three-component mixture of CBZ, *L*G2-Lys and hexylamine and would suggest that CBZ does not impact so

adversely on the overall thermodynamics of assembly of the decylamine system.

Table 2. Thermodynamic parameters extracted from the van't Hoff treatment of VT NMR data in the temperature range of 25−50°C.

Gel	ΔH_{diss} [a]	ΔS_{diss} [b]	ΔG_{diss} [a]
LG2-Lys+C_6NH_2+CBZ	19.6	22.6	12.8
LG2-Lys+$C_{10}NH_2$+CBZ	55.4	141.3	13.3

[a]In kJ/mol; [b]in J/molK

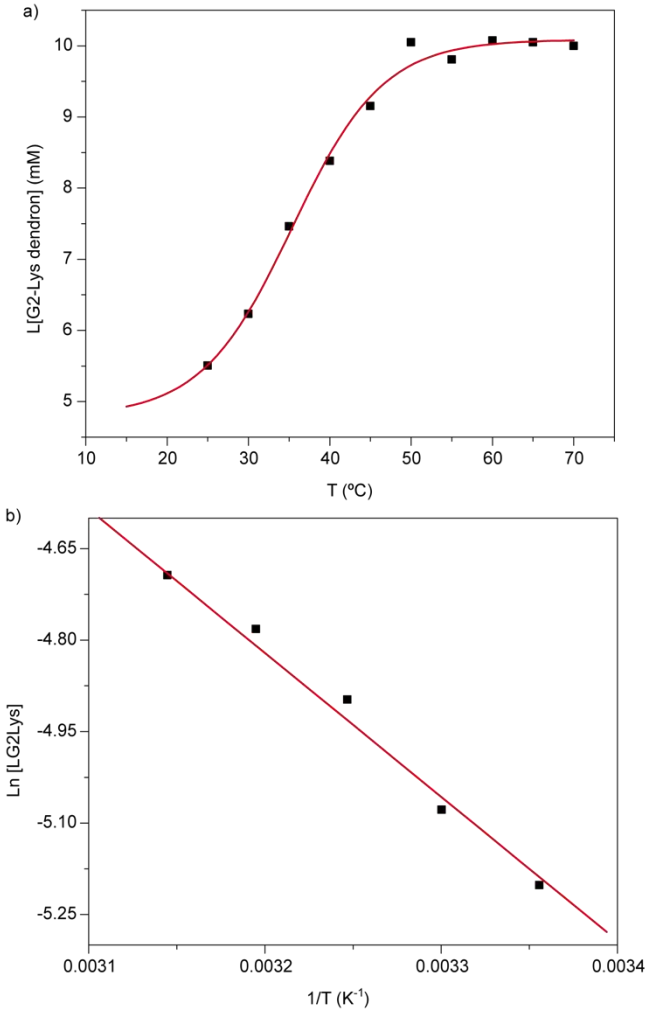

Fig 3. (a) VT NMR quantification of the mobile components in a 1:1:1 mixture of *L*G2-Lys, C6NH_2, and CBZ; (b) Van't Hoff plot of the solubilisation process of the 1:1:1 mixture of *L*G2-Lys, C6NH_2, and CBZ. All the measurements were performed at 10 mM and in toluene-d8.

Competence between drug·amine and G2-Lys dendron·amine interaction. The negative results, regarding both the gelation process and the formation of crystals, obtained in our attempts to crystallize APIs endowed with carboxylic acid groups (ASP and IND) inside G2-Lys/amine organogels suggests a competitive supramolecular process between the three components of the mixture which inhibits self-assembly. It is well established that the primary interaction responsible for forming the two-component complex which underpins the gelation of dendritic Lys-based derivatives and alkylamines is the acid-base interaction between the free carboxylic acid of the Lys moiety and the $-NH_2$ group of the amine – which is mediated by hydrogen bonding supported by potential proton transfer from acid to base.[12,17] The inhibition of gelation by acid-functionalised APIs therefore led us to propose that the supramolecular interaction between the carboxylic acid functional group of the API and the amine might be stronger than that established between the Lys dendron and the amine. To demonstrate this competitive process we calculated the binding constant for the $-CO_2H\cdots NH_2$- pair produced between the *L*G2-Lys dendron and decylamine, a combination that, although still forming such interactions, does not further assemble into a sample-spanning gel at room temperature, and is hence amenable to NMR titration analysis. The binding constant was calculated by ^{1}H NMR titrations in toluene-d8. The titration of a 2 mM solution of decylamine with increasing amounts of the *L*G2-Lys dendron results in the deshielding of the resonances of the methylene groups of decylamine and, especially, the methylene adjacent to the amine group (Figure S14). The binding constant of this supramolecular interaction has been determine by using the fitting program published by Thordarson that utilizes a global analysis of several datasets.[19] The binding constant K_a was calculated by fitting the variation of the chemical shift ($\Delta\delta$) of decylamine (*H* in equation 1) upon increasing the concentration of the dendron (*G* in equation 1). Equation 1 combines the K_a values with the mass balance equations for the total concentrations of the host $[H]_0$, guest $[G]_0$, and the concentration of the final complex *HG*. The calculated value of K_a for the $-CO_2H\cdots NH_2$- pair in the dendron-amine supramolecular motif is 3759 ± 28 M^{-1} (Figure S15).

$$[HG] = 1/2\{([H]_0 + [G]_0 + 1/K_a) - \sqrt{([H]_0 + [G]_0 + 1/K_a)^2 - 4[H]_0[G]_0}\} \quad \text{Eq. 1}$$

We have utilized the same procedure to calculate the binding constant that defines the interaction between IND, as a representative example of an API endowed with a carboxylic acid, and decylamine. As in the interaction between *L*G2-Lys dendron and decylamine, the formation of the $-CO_2H\cdots NH_2$- pair is the driving force of the supramolecular interaction between IND and decylamine. Thus, addition by titration of this amine to a 2 mM solution of IND results in the downfield shift of most of the representative resonances of both the API and the amine. Especially useful for the calculation of K_a are the resonances of IND ascribed to the methylene adjacent to the carboxylic acid (red resonance and red circle in Figure 4), the methoxy group (blue resonance and blue circle in Figure 4) and the methyl group in the pyrrole ring (orange resonance and orange circle in Figure 4). The global fitting of the variation of these three resonances results in a calculated value of 14923 ± 1 M^{-1} for K_a. This K_a value is around four times higher than that calculated for the binding constant between the *L*G2-Lys-dendron and decylamine. Consequently, mixing IND, *L*G2-Lys-dendron and decylamine produces a competitive supramolecular process in which the formation of the $-CO_2H\cdots NH_2$- pair between the API and the amine is thermodynamically favoured. The complex IND$\cdots C_{10}NH_2$ does not crystallize in these experimental conditions

and, in addition, impedes the supramolecular interaction between *L*G2-Lys-dendron and decylamine thus preventing the corresponding gelation.

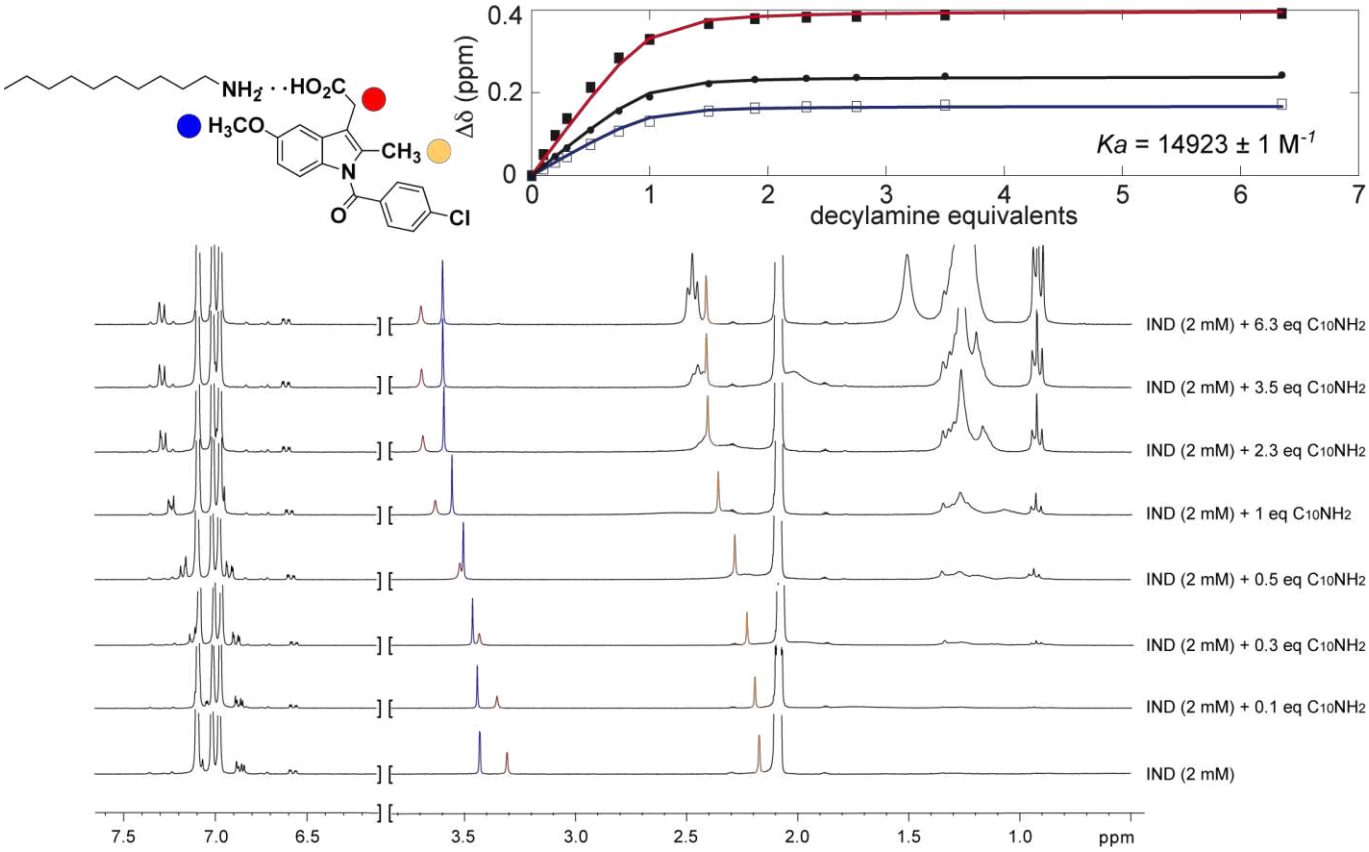

Fig 4. Partial ^{1}H NMR spectra (300 MHz, 298 K, 2 mM, toluene-d8) of IND upon tritration addition of decylamine. The upper part of the Figure shows the chemical structure of IND highlighting the protons utilized for the calculations of K_a and also the isotherms resulting from the titration. The binding isotherms correspond to a 1:1 complexation model by using the methylene adjacent to the carboxylic acid (black squares), the methoxy group (circles) and the methyl group at the pyrrole ring (blue squares).

Conclusions

Two-component gels formed by G2-Lys dendron and alkyl amines have been applied as crystal growth media of APIs. APIs like CAF or CBZ, which do not directly interact with either of the two-components, readily crystallize inside the gel network formed by both *D*G2-Lys and *L*G2-Lys dendrons and hexylamine with no significant difference in the polymorphism of the crystals depending on the chirality of the G2-Lys dendron. The thermodynamic parameters associated with the gelation process for the mixture of CBZ, *L*G2-Lys dendron and hexylamine have been calculated from VT ^{1}H NMR experiments. These experiments demonstrate that both the ΔH_{diss} and ΔS_{diss} are smaller than those calculated for the gel without CBZ indicative that the nanoscale assembly process is less ordered/organised. However, SEM imaging indicates that the fibrillar network is still formed around the API crystals. Interestingly, the presence of CBZ in the mixture of G2-Lys dendrons and decylamine promotes efficient gelation at room temperature, in contrast with the behaviour observed for G2-Lys dendron and decylamine in the absence of API, which only forms toluene gels at -20ºC. Furthermore, the thermodynamic parameters associated with the gelation of this ternary mixture were larger than those associated with the mixture including hexylamine. As such, we can propose synergistic effects in this three component system.

All attempts at crystallization carried out with APIs endowed with a carboxylic acid group, ASP or IND, were unsuccessful. ^{1}H NMR titrations in toluene-d8 demonstrated the competitive process present in the three components mixture of IND, *L*G2-Lys and decylamine to form the corresponding $-CO_2H\cdots HN_2-$ pair that is responsible for the formation of the supramolecular ensembles. Thus, the value of the K_a of the pair *L*G2-Lys dendron and decylamine is 3760 M^{-1}, the K_a of the pair IND and decylamine being 14920 M^{-1}. The latter value demonstrates that the formation of the pair IND-decylamine is thermodynamically favoured and the formation of the corresponding supramolecular complex impedes both the formation of the corresponding organogel and the crystallization of the API – as such, this three-component system has an antagonistic effect.

The results presented herein demonstrate the applicability of two-component gels as crystal growth media of APIs and also

the way in which their performance is responsive to the chemical structures of the APIs in order for both effective gelation and crystallisation to occur. Once again, this demonstrates the tunability of multi-component gels, and the controlled ways in which they can respond in the presence of different additives.

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Multi-component supramolecular gels for the controlled crystallization of drugs: Synergistic and antagonistic effects

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Active pharmaceutical ingredients (APIs) with no carboxylic acid in their structure readily crystallize inside the organogels formed by G2-Lys dendron and aliphatic amines exhibiting a synergistic effect. In contrast, APIs with carboxylic acid exert an antagonistic effect and prevent both the gelation of the mixture and the crystallization of the API.