On-demand Hydrophobic Drug Release Based on Microwave-responsive Graphene Hydrogel Scaffolds

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Abstract: Electromagnetically driven drug delivery systems stand out among stimulus-responsive materials due to their ability to release cargo on demand by remote stimulation, such as light, near infrared (NIR) or microwave (MW) radiation. MW-responsive soft materials, such as hydrogels, generally operate at 2.45 GHz frequencies, which usually involves rapid overheating of the scaffold and may affect tissue surrounding the target location. In contrast, 915 MHz MW penetrate deeper tissues and are less prone to induce rapid overheating. In order to circumvent these limitations, we present here for the first time a graphene-based hydrogel that is responsive to MW irradiation of ν = 915 MHz. This system is a candidate soft scaffold to deliver a model hydrophobic drug. The graphene present in the hydrogel acts as a heat-sink and avoids overheating of the scaffold upon MW irradiation. In addition, the microwave trigger stimulates the *in vitro* delivery of the model drug, thus suggesting a remote and deep-penetrating means to deliver a drug from a delivery reservoir. Moreover, the MW-triggered release of drug was observed to be enhanced under acidic conditions, where the swelling state is maximum due to the swelling-induced pH-responsiveness of the hydrogel. The hybrid composite described here is a harmless means to deliver remotely a hydrophobic drug on demand with a MW source of 915 MHz. Potential uses in biomedical applications were evaluated by cytotoxicity tests.

Introduction

Modern drug delivery techniques offer a promising alternative to the conventional administration of drugs. Many advances have been made in the past few decades concerning smart responsive materials for the controlled delivery of drugs.[1–3] Among them, hydrogels, which are 3D crosslinked polymer networks swollen in water, stand out as biocompatible alternatives that offer wide applicability in the biomedical field.[4,5] The versatility of these materials as smart delivery reservoirs lies in their ability to respond to a variety of stimuli. In this sense, hydrogels can react to biochemical stimuli such as environmental pH, the presence of ions, biomolecules, as well as stimuli of a physical nature, such as electric currents, temperature or magnetic fields.[6–10] Electromagnetic-responsive hydrogels have also been reported. Near Infrared Radiation (NIR) and light serve as innocuous stimuli that can trigger a response from an external source in order to release a desired cargo.[11,12] Microwaves (MW) are electromagnetic waves with frequencies ranging between 300 MHz and 300 GHz and they are particularly interesting as an external stimulus due to their ability to penetrate deeply into living tissue; in this sense, MW radiation has proven useful both for transdermal drug transport and as a skin permeation enhancer.[13–15] However, there are very few examples in the literature regarding materials that respond to microwave radiation, particularly for soft scaffolds.[16] In this respect, Wang *et al.* reported a hydrogel with MW susceptibility (2 W, 2.45 GHz) that converted radiation into localized heat while releasing doxorubicin hydrochloride (DOX) as the temperature rose for tumor ablation therapy.[17] In another example, Rivero *et al.* built a soft MW-sensitive (700 W, 2.45 GHz) polyaniline/poly(N-isopropylacrylamide) (PANI/PNIPAm) copolymer that converted electromagnetic radiation into heat, which was used to induce a sol-gel transition and thus allow tris(2,2'-bipyridine)ruthenium(II) ion (RBPY) release.[18]

The examples reported to date only concern MW radiation of 2.45 GHz as a stimulus for drug delivery applications. However, MW frequencies of 915 MHz could prove beneficial for clinical uses. For instance, the penetration depth of this wave is larger (6–8 cm) than for the 2.45 GHz wave (2 cm),[19] which means that it could be applied for controlled drug delivery systems in deeper organs. In addition, since weakly polar or non-polar substances are poorly heated by the 915 MHz wave, they provide a means to obtain a response while preventing overheating of nearby tissue. It should be noted that microwave dielectric heating takes place as a consequence of dipolar polarization and ionic conduction mechanisms – in contrast to classical heating, which occurs by convection and conduction. This fact results in a rapid internal

heating (in-core volumetric heating) by the direct interaction between the electromagnetic radiation and the sample. In the case of 2.45 GHz MW in particular, these waves produce selective heating of polar substances in the presence of apolar ones.[20] Other ways to enhance the absorption of MW radiation include the use of composite microwave absorbers, i.e., polymeric matrices embedded with nanomaterials with the capacity to absorb MW radiation.[21,22]Among the state-of-the art materials used for this purpose, graphene has proven to be an excellent microwave absorber due to its large π-conjugated structure, high dielectric loss and low density.[23,24]

Based on our knowledge on nanocomposite hydrogels,[25,26] in the work reported here we evaluated graphene-diaminotriazine (G-DAT) hybrid hydrogels as microwave multi-stimulus responsive materials for drug delivery applications. Irradiation with 915 MHz microwaves provides a novel means to trigger remotely the release of cargo. Graphene is an excellent microwave absorber and we envisaged that the presence of this filler would enhance the interaction between the hydrogel and the electromagnetic impulse, thus aiding in the absorption of MW radiation. In addition, the pH-responsiveness of diaminotriazine (DAT) hydrogels (pKa of DAT = 5.15) was simultaneously studied and combined with the microwave trigger in order to study the overall multi-stimulus response on the release of cargo. Furthermore, the MW-induced temperature increase of the hydrogels upon MW exposure was evaluated.

Results and Discussion

In previous studies, we reported that G-DAT hybrid hydrogels enhanced the delivery of a hydrophobic drug through selective disruption of DAT-DAT hydrophobic interactions.[27] This enhancement was caused by the loosening of hydrophobic DAT domains that entrapped the drug, which in turn was caused by the presence of graphene as well as in response to an external acidic medium. The structure of the hydrogels is depicted in Figure 1. The graphene embedded in G-DAT hydrogels was shown to be homogeneously dispersed in the hydrogel matrix, which is a prerequisite for their applicability as microwave absorbers.[28] Based on graphene being an excellent MW absorbing material, in this work we further studied G-DAT hydrogels as drug delivery carriers triggered by MW irradiation at 915 MHz. The ability of these materials to dissipate the heat generated upon MW exposure was also evaluated.

Characterization of the hydrogels

The Few-layer graphene introduced in the DAT-based hydrogels was prepared by a mechano-chemical exfoliation protocol previously reported in our group.[29,30] Raman spectroscopy shows that the graphene flakes have a low amount of defects as reflected by an I_D/I_G ratio of 0.38. Additionally, FLG has an average number of layers $N_G = 4$.[31] The nanomaterial shows less than 4% oxygen content, as corroborated by elemental analysis and TGA. TEM images further complemented the characterization of the material (Figure S1).

Further characterization of the hydrogels is shown in Figure 2. FTIR spectroscopy (Figure 2a) reveals that DAT and 0.5G-DAT hydrogels (blue and green lines, respectively) display the characteristic C=N and C-N vibrations of the VDAT monomer (orange line), at 1640 and 1511 cm^{-1},[32] whereas the N-H stretching at 3310 and 3142 cm^{-1} of the monomer shifts to 3327 and 3186 cm^{-1}, respectively, in both DAT and 0.5G-DAT hydrogels. This shift is attributed to the H-bond formation of DAT and the interactions with graphene moiety as it has already been shown in literature: on the one hand DAT-DAT pairs have been observed to self-associate *via* hydrogen bonds through the terminal N-H when VDAT is polymerized into PVDAT.[33]

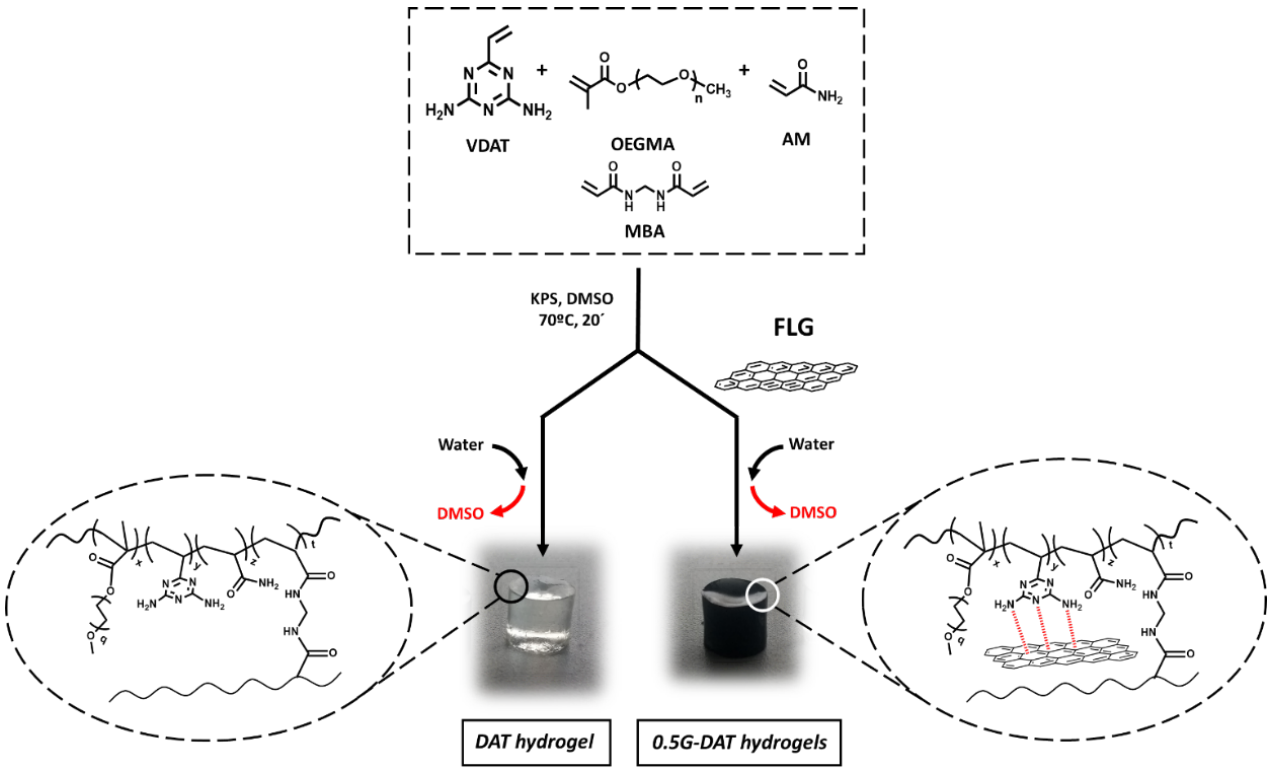

Figure 1. Structure of DAT and G-DAT hydrogels. After initial polymerization in DMSO, the organogels are immersed in water and the organic solvent is phase inverted, yielding the corresponding DAT-based hydrogels

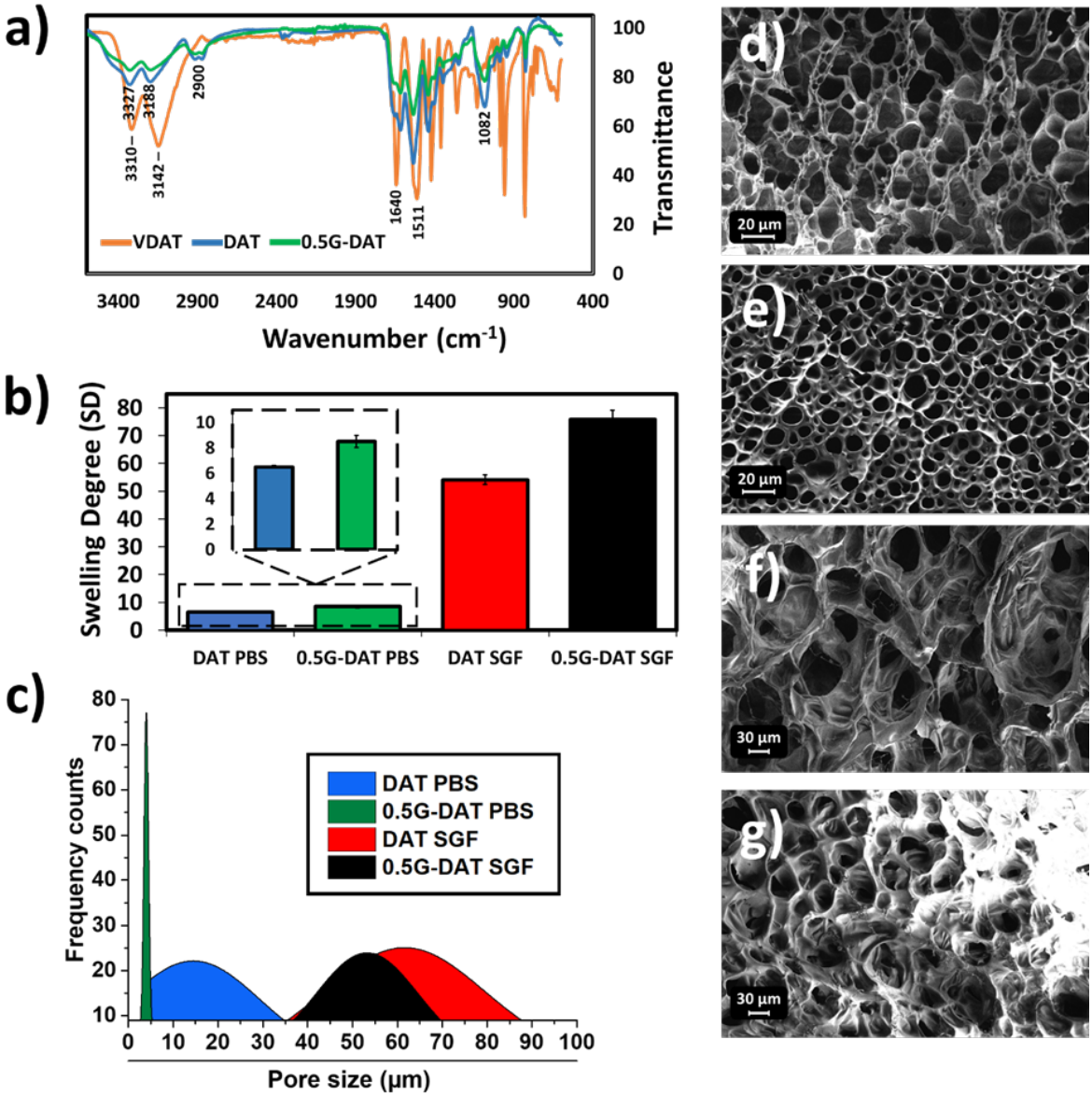

Figure 2. Characterization of DAT-based hydrogels. a) FT-IR spectra b) Maximum swelling degree in PBS (Phosphate Buffered Saline) and SGF (Simulated Gastric Fluid) media c) Pore size distributions in PBS and SGF media d) SEM images of DAT and e) 0.5G-DAT hydrogels in PBS media and f) DAT and g) 0.5G-DAT in SGF media

On the other hand, graphene-NH_2 interactions have also been demonstrated between the terminal N-H bonds of triazine derivatives and the surface of graphene sheets.[34,35] Finally, the stretching vibrations of -CH_2O- and C-O at 2900 and 1082 cm^{-1} reveal the presence of oligoethylene glycol moieties in the DAT-based hydrogels, which are absent in the VDAT monomer.

Swelling studies of DAT-based hydrogels were performed both in PBS (Phosphate Buffer Saline, pH = 7.4) and SGF (Simulated Gastric Fluid, pH = 1.2). Although the diaminotriazine molecule protonates at low pH (pK_a =5.15), the SGF buffer was chosen as an acidic medium in order to mimic physiological environments. As expected, DAT hydrogels were shown to increase their swelling degree up to 10-fold in SGF buffer (Figure 2b),[27] proving their pH-response to acidic media. Under these conditions, DAT moieties are protonated and repel each other, thus increasing the water content inside the polymer network. Likewise, graphene DAT hybrids displayed higher swellings

than DAT homologues (Figure 2b). As it was observed in previous studies[27] in diaminotriazine-based hydrogels in neutral media, the DAT domains act as "water barriers", due to their intrinsic hydrophobic nature, and restrict water entry inside the network. When graphene is introduced, the nanomaterial disrupts the DAT aggregates through π-π and graphene-NH_2 interactions between DAT and graphene layers, and this fact consequently increases the swelling degree (SD).[27]

Pore size distributions of the hydrogels in their maximum swollen state show polydisperse average sizes for DAT hydrogels in PBS media (15±14.5 μm) (Figure 2c, blue). Since DAT molecules tend to aggregate into amorphous domains, porous distributions in DAT-based hydrogels tend to be heterogeneous.[36] Interestingly, sharper distributions were observed for 0.5G-DAT hybrids (3.99 ±0.1μm) (Figure 2c, green). This narrowing of the pore size is attributed to the effect that graphene exerts in the hydrogel: DAT molecules align into extended 2D hydrogen-bonded films on top of the graphene surface and this event reorganizes the porous structure of the hybrids.[27] In SGF media, rather similar pore size distributions were observed for DAT and 0.5G-DAT hydrogels (Figure 2c red and black, respectively). It is logical that in their protonated state, where the DAT molecules are distant from each other, the DAT molecules are not available for aligning on top of graphene sheets, therefore no significant rearrangement on the porosity is observed when graphene is incorporated in the hydrogels. Figures 2d-g) show representative SEM images of DAT and 0.5G-DAT hydrogels in PBS and SGF media.

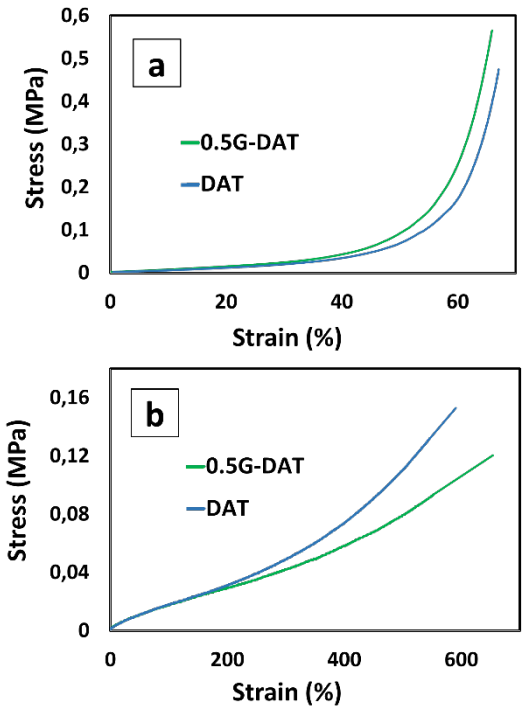

Figure 3. Mechanical tests for DAT-based hydrogels a) Compressive and b) tensile stress-strain curves

Mechanical tests were also performed to study the impact of graphene on the structure of the hydrogels. 0.5G-DAT hydrogels showed lower compressive strains than DAT analogues (Figure 3a) and 35% higher Young moduli (59 kPa *vs* 43 kPa), pointing out the stiffer nature of the graphene hybrids. Previous work in our group showed that an increase in graphene contents lead to stiffer soft materials.[37,38] Further, 0.5G-DAT hydrogels appeared more ductile than DAT analogues (Figure 3b) with both hydrogels having similar toughness values (320 *vs* 339 $kJ.m^{-3}$). Since graphene disrupts the DAT strengthening H-bonding network, it is possible that 0.5G-DAT hybrids stretch farther than DAT analogues.

MW (v = 915 MHz) fixing conditions

The interaction between any biomaterial with a high water content and MW radiation tends to generate heat. For applicability in the biomedical field, such as bio-implants, in order to avoid heating nearby tissue, this overheating must not surpass physiological body temperatures, i.e., 36–38 ºC. In an effort to adapt our scaffolds to the MW exposure, we first focused on setting the irradiation conditions so that MW-induced temperatures of the hydrogels reached no higher than 38 ºC.

The MW-induced temperature increase of the DAT-based hydrogels was observed to be strongly dependent on two parameters: incident power (P_{inc}) and irradiation times (t_{ir}). For this purpose, we first evaluated the temperature-power dependence with respect to time of DAT hydrogels (see Figure 4a). This graph shows a notable temperature increase as a function of time and incident power. After two minutes, hydrogels irradiated with P_{inc} = 1 kW reached almost 60 ºC, whereas temperatures over 90 ºC were recorded for P_{inc} = 2 kW and 3 kW. In addition, the temperatures were observed to increase linearly for P_{inc} = 1 kW, while for higher incident powers this trend was more pronounced and eventually became non-linear. In particular, for P_{inc} = 3 kW, the temperature values reached a plateau after almost 80 minutes irradiation, after which they did not exceed 90–95 ºC.

Interpolation at T^a = 38 ºC on this graph provides the desired irradiation times t_{ir}, before the hydrogels reached 38 ºC upon MW irradiation at increasing P_{inc} (Figure 4b). For P_{inc} = 1 kW, 2 kW and 3 kW, t_{ir} values of approximately 60", 30" and 15" were recorded, respectively, before hydrogels reached this temperature. It was observed during the irradiation experiments that for $P_{inc} \geq 3$ kW bubbles formed in the hydrogels and signs of structural damage were evident inside the network as a consequence of the very fast overheating process.

For this reason, and in order to avoid exceeding physiological temperatures, only P_{inc} = 1 kW for t_{ir} = 60" and P_{inc} = 2 kW for t_{ir} = 30" were evaluated as irradiation conditions for MW-induced drug delivery studies. Since the hydrogels were immsersed in PBS media during MW exposure, the free buffer was also irradiated in order to observe whether the temperature difference between the hydrogel and the buffer upon MW exposure would be significant (Figure S2). Similar temperature profiles were recorded independently for hydrogel and free buffer for MW irradiations of P_{inc} = 1–2 kW, whereas for P_{inc} = 3 kW this difference increased

markedly. Thus, for MW exposure of P_{inc} = 1–2 kW the occurrence of heat transfer mechanisms other than MW-induced temperature increase, such as convection or conduction from the hydrogel to the media or viceversa, were ruled out.

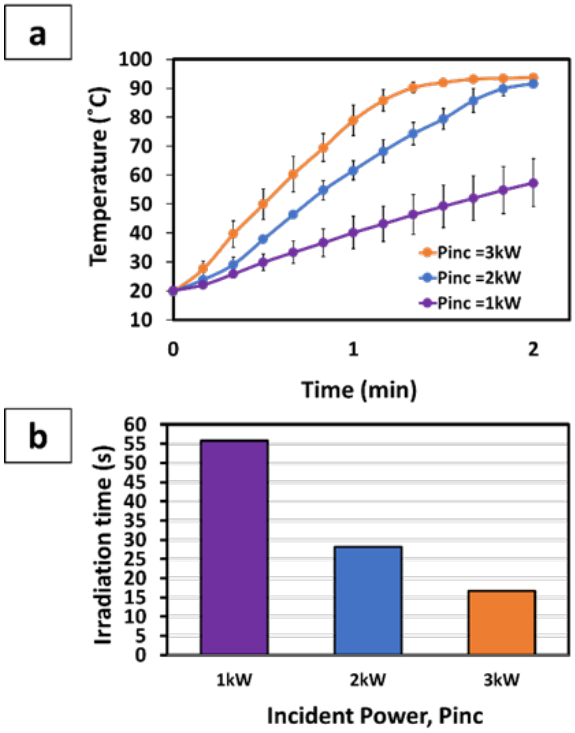

Figure 4. MW irradiation for DAT hydrogels at increasing Incident power,P_{inc} a) MW-induced temperature increase for irradiation times, t_{ir} = 0–120" (b) irradiation times, t_{ir}, for T^a = 38ºC

Having fixed the MW irradiation conditions, these were preliminary tested on the MW-triggered drug release of DAT hydrogels in PBS media (Figure 5). Dried hydrogel samples were placed in an imipramine/PBS solution (2.5 mg/mL) until maximum swelling was achieved, reaching drug loading values of 29.8% for DAT hydrogels. Imipramine was chosen as a model hydrophobic drug, as tested on previous studies.[27] Samples were then irradiated for four cycles, corresponding to the first 3 h of the experiment and compared with control reference, which was left to release drug in the absence of MW stimulus by simple difussion. It was observed that hydrogels under MW irradiation released higher % drug than the control reference: after the first hour, samples irradiated at P_{inc} = 2 kW surpassed those of P_{inc} = 1 kW, and eventually released 10% more drug than the control reference after 6 h. These experiments demonstrated the potential of the 915 MHz microwaves in inducing drug release from a delivery reservoir, which until now had not been reported. Encouraged by these results, we selected P_{inc} = 2 kW for t_{ir} = 30" as MW irradiation conditions for an extended period of 24 h *in vitro* drug release, as discussed further.

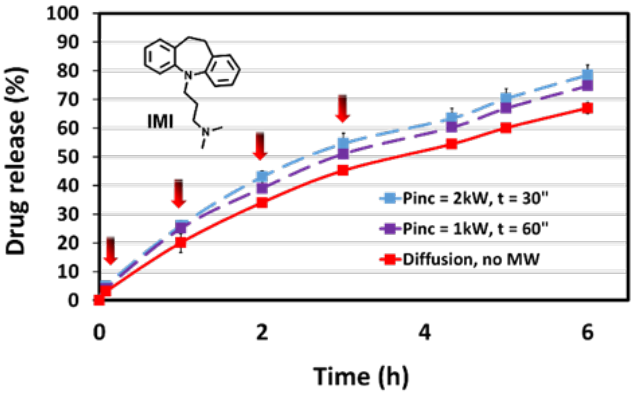

Figure 5. MW-induced imipramine delivery of DAT hydrogels under different conditions in PBS media. Red arrows depict each cycle of MW irradiation; dashed and straight lines represent release profiles in the presence and absence (by simple diffusion) of MW stimulus, respectively.

Effect of graphene under MW irradiation

Few-layer graphene (FLG) is one of the most widely used microwave absorbing materials in polymer-filled composites, particularly when homogeneously dispersed in polymer matrices.[28] In order to determine the capacity of graphene hybrids to absorb MW radiation and dissipate heat, we first studied the MW-induced temperature increase of 0.5G-DAT hydrogels (0.5% w/w filled graphene) upon irradiation at P_{inc} = 2 kW in PBS media (Figure 6a), which were the optimal conditions observed for MW-induced drug delivery for DAT hydrogels. The results show that 0.5G-DAT hydrogels are less susceptible to overheating than DAT hydrogels, particularly for longer times, as the temperature reached was 15 ºC lower for t_{ir} ≥ 90" than the pristine counterparts. Extrapolation at t_{ir} = 30" (the t_{ir} chosen for MW exposure at P_{inc} = 2 kW before DAT hydrogels reached T^a = 38ºC) shows graphene hybrids barely reach 33 ºC, which is several degrees below DAT hydrogels irradiated under the same conditions (Figure 6b). The results obtained demonstrate that graphene embedded into DAT hydrogels efficiently dissipates heat upon irradiation with MW of 915 MHz, which makes them particularly attractive as MW-responsive soft materials for remote drug delivery by MW stimulation.

MW-triggered *in vitro* drug delivery studies

Pre-drug loaded DAT and 0.5G-DAT hydrogels (29.8 and 36.6% drug loadings, respectively) were irradiated in PBS media under the selected conditions (P_{inc} = 2 kW, t_{ir} = 30"/cycle) for 4 cycles during the first 3 h. The hydrogels were left to release the drug up to 24 h in the experiment (Figure 7). DAT and 0.5G-DAT series exposed to MW irradiation (dashed blue and green, respectively) were observed to release higher % drug than their respective controls (blue and green), whereas the respective release rates tended to level off after longer periods. After the fourth cycle both series had released up to 5% more drug than the respective controls (Figure 7, inset), which indicates that the influence of graphene in MW-induced drug delivery is rather negligible in this medium.

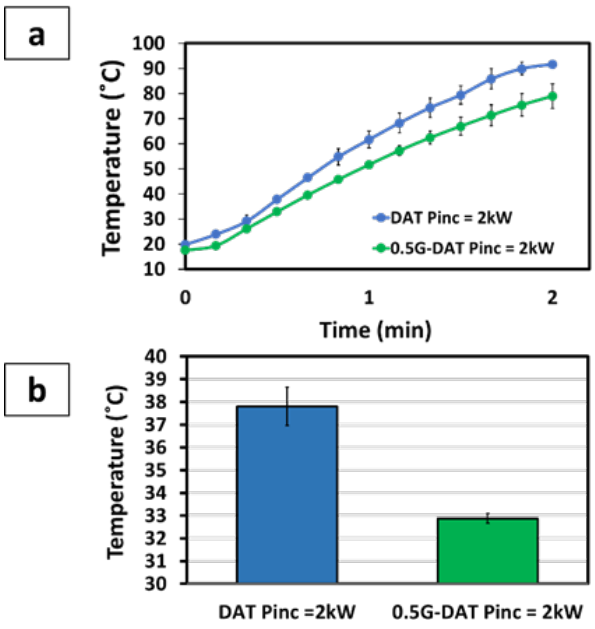

Figure 6. MW-induced temperature increase for DAT and 0.5G-DAT hydrogels at Incident Power, P_{inc} = 2 kW (a) t_{ir} = 0–120" (b) t_{ir} = 30"

The release of drug, however, is markedly enhanced by the presence of graphene, regardless of the microwave exposure. An increase in the drug release of ~20% was observed for 0.5G-DAT when compared to the DAT controls after 24h, when both release profiles are steadied. In previous studies[27] G-DAT hydrogels enhanced the release of a model hydrophobic drug as a result of the interactions between graphene sheets and diaminotriazine moieties: graphene sheets were shown to interfere with the hydrophobic DAT-DAT domains responsible of entrapping the drug, altering the porous structure and thus facilitating diffusion by helping relieve the strain through the network.

So far, the sole effect of 915 MHz microwaves on the release of a model drug in PBS media was tested. Now, we consider the multi-stimulus effect of both acidic pH and MW on the release rates. As reported in previous publications by our group, DAT-based hydrogels show pH-responsive behaviour in acidic environments.[27] The hydrogels were found to increase their swelling degree (SD) 10-fold in SGF (simulated gastric fluid, pH = 1.2) with respect to PBS media (pH = 7.4). For this reason, in order to compare the effect of the MW on the release of model drug in two different swollen states, the MW-induced release experiments were also conducted in SGF media. The multi-stimulus responsive release of the drug for DAT and 0.5G-DAT hydrogels are shown in Figures 8a and 8b, respectively. As mentioned previously, release rates triggered by MW in PBS media eventually match their respective controls in the absence of MW exposure, both for DAT and 0.5G-DAT hydrogels. In contrast, MW irradiation in SGF media notably enhances the release of drug with respect to their respective controls throughout the whole 24 h experiment (red and black lines). In fact, this can be particularly appreciated throughout the four cycles of MW irradiation, i.e., during the first 3 h of the experiment. As mentioned before, after the fourth cycle of MW exposure in PBS media, both DAT and 0.5G-DAT hydrogels released only 5% higher rates than the control reference (Figures 8a,b inset, blue and green lines), whereas in SGF media this difference is greater than 6% and 10% for DAT and 0.5G-DAT hydrogels, respectively (Figures 8a,b inset, red and black lines). It can therefore be stated that the improvement in the MW-induced drug delivery is more pronounced in SGF media than in PBS media, particularly for G-DAT hydrogels.

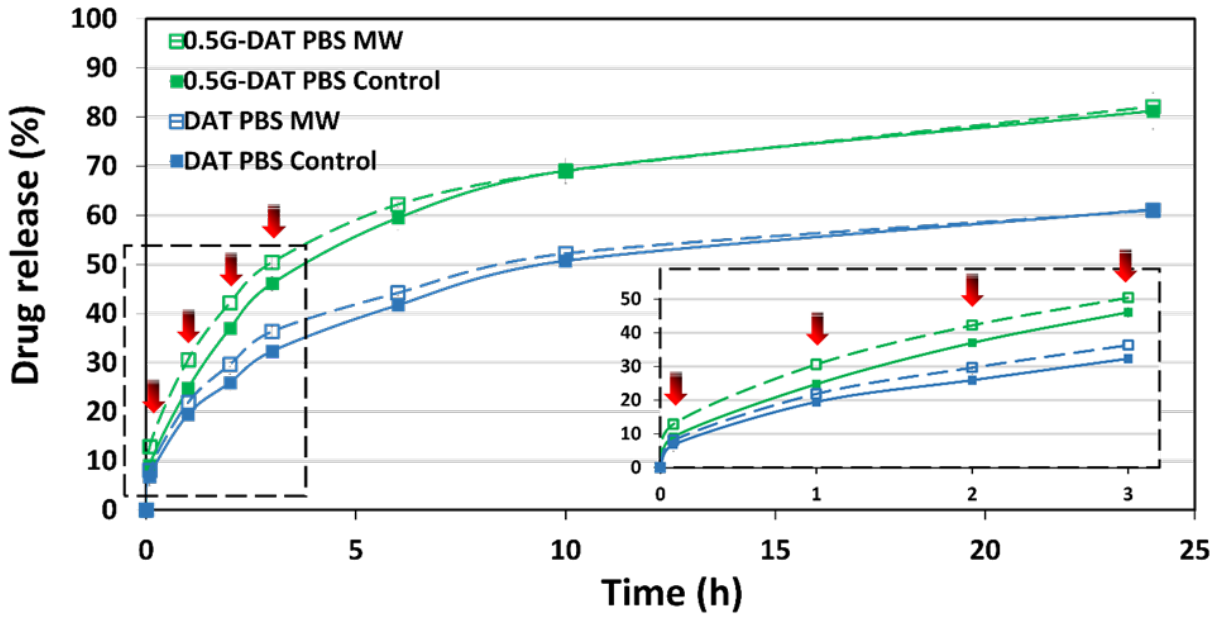

Figure 7. 915 MHz Microwave-triggered Imipramine release by DAT and 0.5G-DAT hydrogels in PBS media. Red arrows depict each cycle of MW irradiation; dashed and straight lines represent release profiles in the presence and absence (by simple diffusion) of MW stimulus, respectively.

The swelling degree is a parameter that quantifies the maximum amount of water that a hydrogel can incorporate within the network; The evolution of the SD of the DAT-based hydrogels in PBS and SGF media within the first three hours of the experiment is represented in Figure 9a, i.e., the same time over which the hydrogels were exposed to MW radiation in the delivery experiments. The results for SD experiments up to 24 h are shown in Figure S3. In PBS media the DAT hydrogels show the lowest SD values (Figure 9a, blue line). In this state, the SD is governed by hydrophobic interactions: hydrogen bonds and π-π stacking between DAT-DAT molecules act as 'water barriers' and restrict water entry (Figure 9b).[33,36] However, two independent factors were observed to disrupt these DAT hydrophobic aggregates inside the water-swollen hydrogels: On the one hand, graphene forms favourable π-π and NH_2-graphene interactions with the DAT moieties. This interferes with the DAT-DAT hydrophobic domains mentioned above[34,35]and partially disrupts them, thus increasing the SD values[27] (Figure 9a, green line). On the other hand, immersion in strongly acidic media (SGF, pH = 1.2) increased the SD of both DAT and 0.5G-DAT hydrogels (Figure 9a, red and black lines). Since DAT-based hydrogels are pH-responsive (pKa VDAT = 5.15), immersion in such media protonates the DAT residues and this breaks the hydrogen bonds between them. This in turn leads to expansion of the cationic network due to repulsive forces, which leads to higher SD values and an increase in their pore sizes. As expected, 0.5G-DAT hybrids in SGF media showed the highest SD values, since both graphene and the external acidic pH disrupt DAT hydrophobic interactions and cooperatively increase the swelling capacity of the hydrogel (Figure 9c).

Based on the results observed in Figures 7-9, a mechanism of the MW-induced drug release in these hydrogels can then be proposed. In aqueous neutral media a hydrophobic drug, such as IMI, will be trapped in the network due to π-π stacking and hydrogen bonding interactions with the DAT matrix and it will be slowly released from the hydrogel. In fact, previous studies in our group reported DAT hydrogels to be suitable reservoirs for efficient loading and release of hydrophobic drugs.[27] In this scenario, when the MW trigger is applied, the polar functional groups of the hydrogel are likely to oscillate with the wave.[39]

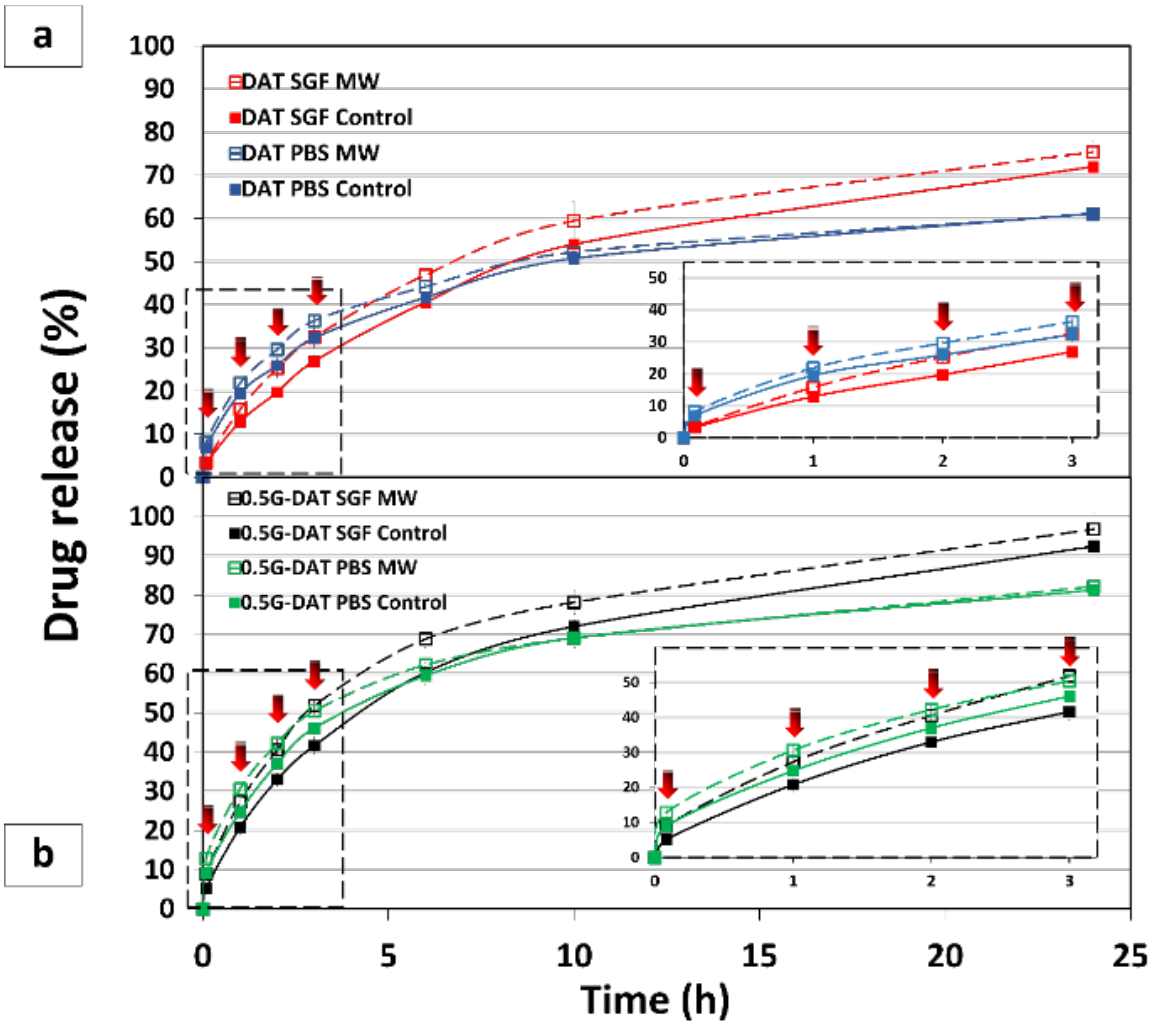

Figure 8. Multi-stimuli-responsive Imipramine release of (a) DAT and (b) 0.5G-DAT hydrogels. in SGF (Simulated Gastric Fluid) and PBS media. Red arrows depict each cycle of MW irradiation; dashed and straight lines represent release profiles in the presence and absence (by simple diffusion) of MW stimulus, respectively.

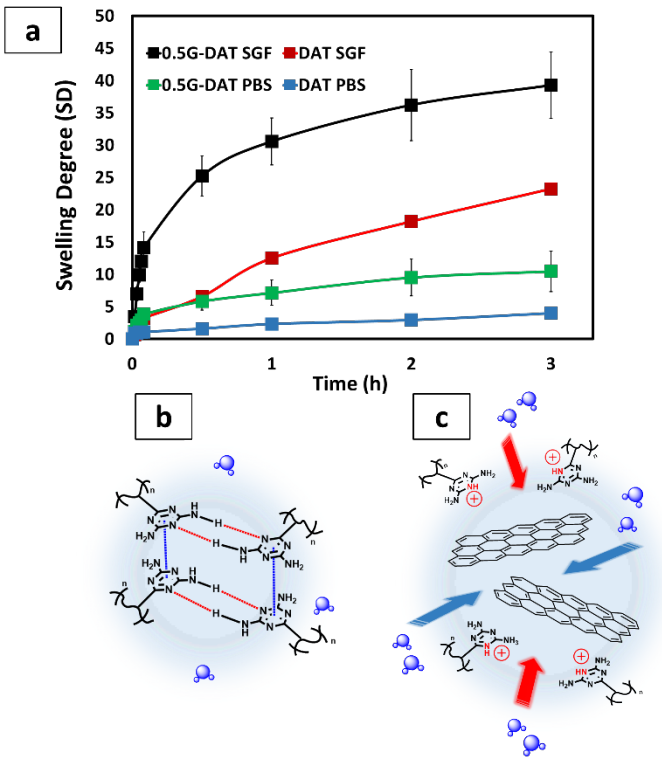

Figure 9. (a) Evolution of swelling degree (SD) with time for DAT-based hydrogels (b) depiction of DAT hydrogel in PBS media (c) 0.5G-DAT hydrogel in SGF media

The hydrogen bonds that hold the DAT molecules together, will then disrupt following DAT free oscillation which open pathways for the release of the hydrophobic drug into the medium (Figure 10a). On the other hand, DAT-DAT π-π stacking and DAT-DAT hydrogen bonds are disturbed in the presence of graphene and SGF media, respectively. When 0.5G-DAT hybrids are subjected to MW irradiation in SGF media, the MW- induced dipolar polarization of DAT groups will be further enhanced[40] since DAT residues are protonated under this acidic pH. Altogether, the contribution of the MW stimulus on the release of IMI is expected to be greater in SGF media and when graphene is incorporated in the network (Figure 10b) as observed from the results in Figure 8.

To confirm this hypothesis, we performed a drug release experiment where IMI drug was loaded in a DAT-free hydrogel consisting of crosslinked acrylamide (AM), previously reported in our group,[37] in the presence and absence of MW irradiation in PBS and SGF media. Upon MW irradiation of the drug-loaded AM hydrogels, no difference was observed in the release of drug between controls and MW-irradiated hydrogels in both buffered media (Figure S4). These results endorse that the drug release improvement observed with the 915 MHz MW stimulus is due to selective disruption of drug-hydrogel interactions, possibly due to hydrogen bonding disruption of DAT dipoles when subjected to MW irradiation

At the same time as the MW-mediated drug release studies, the MW-induced temperature increase of the hydrogels resulting from the four-cycle MW exposure was measured.

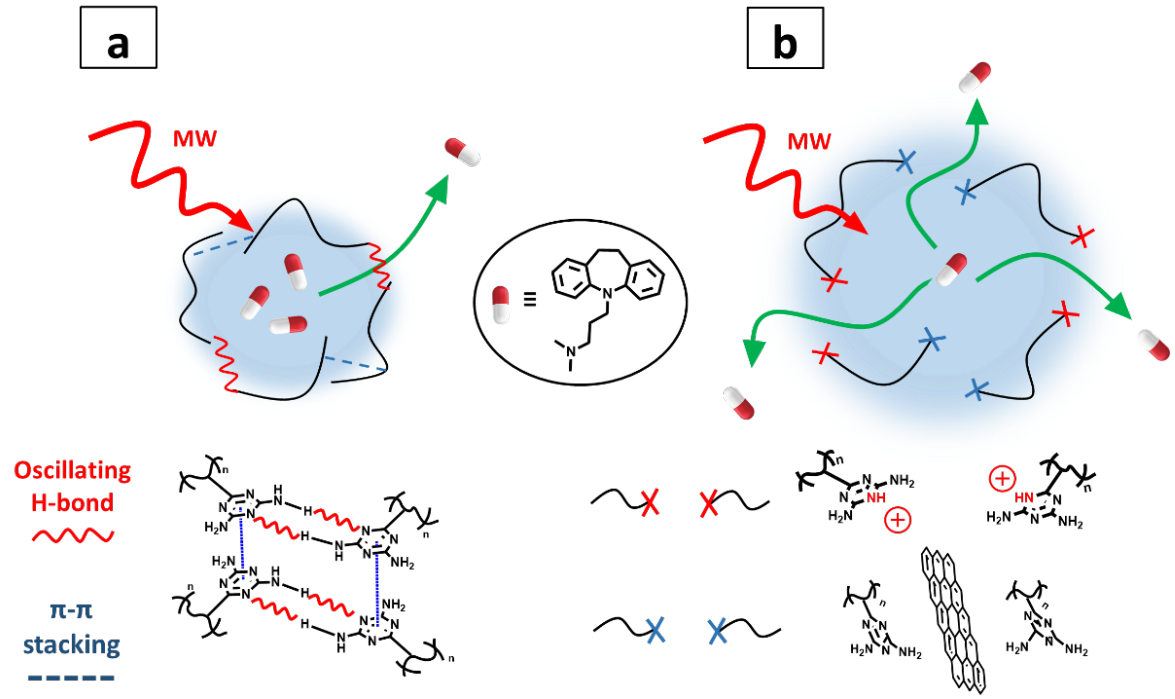

Figure 10. Proposed mechanism for the interaction between 915 MHz MW and (a) DAT hydrogel in PBS (b) G-DAT hydrogel in SGF media

After each irradiation cycle, the hydrogels increased in temperature due to the interaction between the MW and the water molecules inside the network. In PBS media (Figure 11), however, the temperature of 0.5G-DAT hydrogels did not exceed 38 ºC throughout the four cycles, whereas DAT hydrogels in the absence of graphene reached almost 50 ºC after the third irradiation cycle (Figure 11, green and blue lines, respectively). This finding shows that graphene embedded in the hydrogel network helps to avoid a rapid temperature increase of the scaffold upon MW exposure.

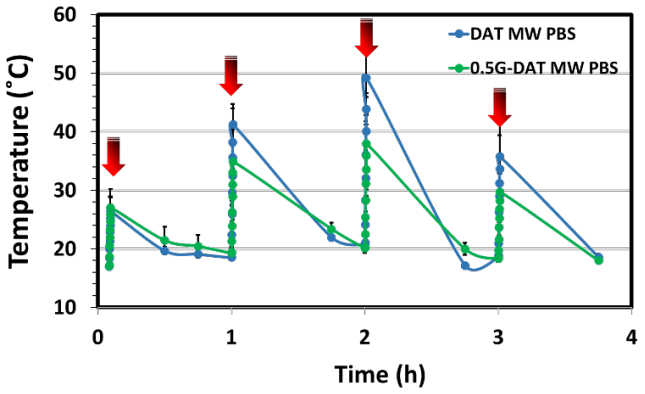

Figure 11. MW-induced temperature increase for four cycles of MW exposure (P_{inc} = 2 kW, t_{ir} = 30"/cycle) of DAT-based hydrogels in PBS media

It has previously been reported that the conjugated π structure of graphene behaves as a net electric dipole and this allows efficient microwave absorption, as well as other mechanisms such as interfacial polarization between the filler and polymer matrix.[41,42] This may account for a greater MW absorption by the filler than by the hydrated network and therefore less heat is generated by friction of freely oscillating water molecules. This finding helps envisage graphene-DAT hybrids as candidates for MW transdermal applications, such as skin patches. One of the main hurdle, concerning transdermal drug delivery, is overcoming the barrier property of the stratum corneum, which naturally hinders permeation of biomedical compounds.[43] In order to circumvent this, microwaves have been used as effective skin permeation enhancers to improve skin permeability.[13] However, both the scaffold and the skin surrounding target site are at risk of overheating, as a consequence of irradiation, and cause skin charring. This is particularly important for 2,45 GHz wavelengths that generate heat by dipolar relaxation processes.[19] The hybrid materials reported here reveal that graphene embedded in the scaffold effectively dissipates the MW-induced heat: 0.5G-DAT hybrids reached temperatures no higher than 32ºC per irradiation cycle, which is below temperatures that may cause skin damage (~38ºC), while still improving the release of drug under the MW stimulus. In addition, the 915 MHz wave helps reach deeper tissues than the 2,45 GHz wave, which can help permeate farther skin sections. In sum, these materials seem promising for controlled transdermal drug delivery applications and further skin therapy in the biomedical field.

The MW-induced temperature increase in SGF media (Figure S5) was found to be similar for both DAT and 0.5G-DAT hydrogels, with temperatures higher than 38 ºC reached. This is somehow expected since the highly swollen and positively charged network of the DAT-based hydrogels in this medium favours dipole oscillation with the MW radiation, as explained previously, which is converted into heat despite the counter dissipation effect of graphene.

In vitro cell viability evaluation

To characterize the biomedical potential of these materials, DAT and G-DAT hydrogels were used to support the growth of SH-SY5Y cells, a human neuroblastoma cell line (see representative images in Figure 12). Under our experimental conditions, lyophilized DAT hydrogels previously swollen in SGF medium significantly presented more living cells that those previously swollen in PBS medium (p=0.019). This is consistent with the pore size distribution of the hydrogels in both media (Figure 2c).

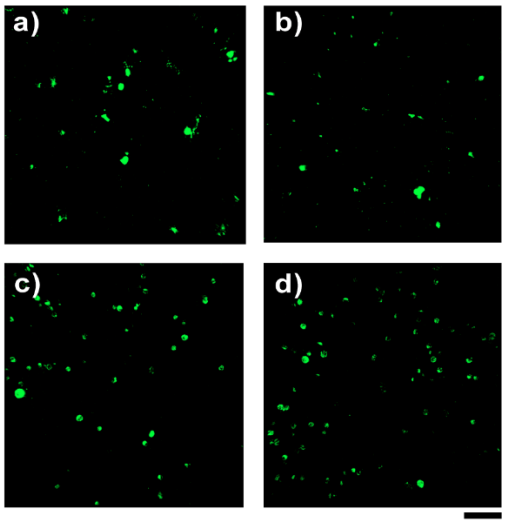

Figure 12. Representative fluorescence confocal images of human neuroblastoma cells (SH-SY5Y cells) grown under different experimental conditions. Calcein-AM was used as cell-permeant dye to determine cell viability (green). a) DAT PBS, b) 0.5G-DAT PBS, c) DAT SGF, d) 0.5G-DAT SGF. Scale bar = 100 µm.

Furthermore, according to previous research,[37,44] the presence of graphene inside the hydrogel facilitates cell adhesion (Figure 13). There was a significant increase in the number of living cells in 0.5G-DAT SGF compared to DAT PBS (p=0.009). Our results demonstrate that graphene hydrogels previously swollen in SGF medium are suitable biocompatible scaffolds with promising applicability in the biomedical field.

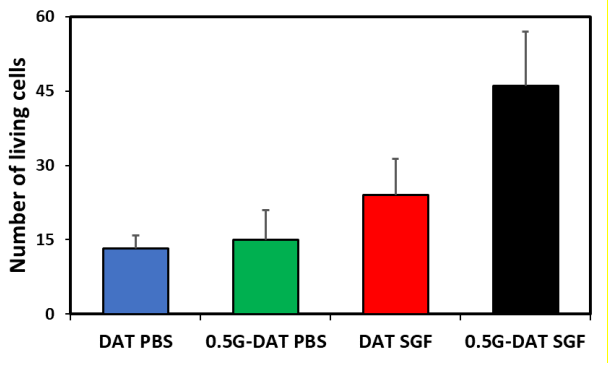

Figure 13. Effect of hydrogel on the number of viable cells. Living cells were stained using Calcein-AM and the number of living cells were quantified after fluorescence image acquisition. Data are Mean value ± Standard Error.

Conclusion

The first multi-stimulus soft material that is responsive to microwaves of v = 915 MHz has been developed. The hybrid graphene-diaminotriazine (G-DAT) hydrogel responds to microwave irradiation and enhances the release of a model hydrophobic drug, particularly under acidic conditions. In contrast to 2.45 GHz microwaves, the penetration depth of 915 MHz frequencies is greater and expands the scope of these proof-of-concept materials to deeper organs. The hybrid nature of the hydrogel was key to its functionality: the presence of graphene helps to dissipate the heat generated during irradiation, thus reducing the risk of overheating the nearby tissue, while the introduction of DAT residues provides pH-responsiveness, which synergistically enhances the release of model drug when the MW-trigger is applied. This cooperative behaviour makes these materials promising drug reservoirs that are able respond to an acidic environment while simultaneously responding to an electromagnetic tissue-penetrating stimulus to release a drug on demand without harming nearby organs. Preliminary studies confirmed that the hybrid hydrogels showed adequate biocompatibility for further applications.

Experimental Section

Materials and reagents

Poly(ethylene glycol) methyl ether methacrylate (OEGMA, Mn = 950), acrylamide (AM), N,N′-methylenebis(acrylamide) (MBA), potassium peroxydisulfate (KPS), epichlorohydrin (EPI), sodium disulfide, melamine and PBS (Phosphate Buffered Saline) were purchased from Sigma-Aldrich as reagent-grade materials. Imipramine hydrochloride (IMI) and 2,4-diamino-6-[2-(2-methyl-1-imidazolyl)ethyl]-1,3,5-triazine (2MA) were purchased from TCI chemicals. Graphite powder was acquired from Bay Carbon Inc. (SP-1 reference). SGF (Simmulated Gastric Fluid) was prepared from a 0.063 M solution of HCl. Culture media and plates used to obtain and maintain cellular cultures were acquired from Thermo Fischer (MA USA).

Preparation of few-layer graphene (FLG) powders

The mechanochemical exfoliation of graphite was performed by ball-milling.[29,30] A 30 mg mixture of graphite/melamine (1:3) was ball-milled at 100 rpm for 30 minutes. The solid was then dispersed and sonicated in 20 mL of ultrapure water; the dispersion was placed in dialysis membranes (Spectrum labs, 6–8 kDa MWCO) and dialyzed against hot water (70 ºC), with the aqueous medium changed every two hours until melamine was no longer detected. The dispersion was then left to stabilise for five days in order for the graphite to settle down and this was then removed from the supernatant. The resultant aqueous graphene suspension was freeze-dried at –80 ºC and 0.05 mbar and the resulting few-layer graphene powders were collected and characterised.

Preparation of 2-vinyl-4,6-diamino-1,3,5-triazine (VDAT)

The synthesis of VDAT was carried out according to a patented procedure.[45] 2,4-Diamino-6-[2-(2-methyl-1-imidazolyl)ethyl]-1,3,5-triazine (0.17 mol) was suspended in 75 mL of deionized water. Epichlorohydrin (0.17 mol) and sodium disulfide (0.0017 mol) were added and the mixture was heated under reflux for three hours. The crude product was washed with cold water, filtered under vacuum and dried in a desiccator for two days to give a colourless pure solid.

Preparation of DAT hydrogels

The synthesis of DAT hydrogels was carried out previously in our group.[27] VDAT (150 mg/mL), OEGMA (135 mg/mL), AM (135 mg/mL), cross-linker MBA (2 mg/mL) and KPS initiator (2 mg/mL) were dissolved in DMSO and the mixture was cast into silicon moulds at 70 ºC for 20 min. The organogels were washed thoroughly in deionized water until all unreacted monomer had been washed out. The samples were then dried in an oven at 40ºC during 2 days at open atmosphere to obtain the desired xerogels.

Synthesis of G-DAT hydrogels

The synthesis of G-DAT hydrogels was carried out in similar manner to the DAT hydrogels, but an organic dispersion of few-layer graphene (FLG) in DMSO was used as the polymerization medium. 0.5G-DAT hydrogels were prepared from 0.5% w/w (2.1 mg/mL) FLG loadings.

Preparation of AM hydrogels

AM monomer (200 mg/ml), crosslinker MBA (0.2 mg/ml) and KPS initiator (0.4 mg/ml) were dissolved in water under stirring at room temperature. The mixture was then casted in a glass vial and heated in an oven for 1h at 75ºC. The hydrogels were washed thoroughly in deionized water until all unreacted monomer had been washed out. The samples were then dried in an oven at 40ºC during 2 days at open atmosphere to obtain the desired xerogels.

FT-IR spectroscopy

Dried xerogel samples were pulverized and measured in a FT-IR, IRAffinity-1S Shimadzu spectrophotometer in a 400-4000 cm^{-1} range.

Scanning electron microscopy (SEM) imaging

Freezed-dried samples were first lyophilised in a Telstar Lyoquest freeze dryer. The porosity was then analysed by SEM imaging using a Gemini SEM 500 from Zeiss. Samples were introduced in the microscope and imaged at an accelerating voltage of 2–3 kV. The pore sizes were then measured according to the images obtained.

Swelling studies

Swelling studies were performed by weighing swollen hydrogel pieces in PBS or SGF media. The weights were registered at defined time intervals until samples reached constant weight. Prior to weighing, the samples were placed on filter paper to remove excess water. The swelling degree (SD) was calculated according to the following formula:

$$SD = \frac{W_t - W_0}{W_0}$$

Where W_0 and W_t are the initial weight and weight at time t, respectively. Three samples were weighed for each measurement.

Mechanical properties

Mechanical tests were performed with a Mecmesin Multitest 2.5-i dynamic mechanical analyser. Compressive tests were carried out compressing uniaxially 1.05 cm x 1 cm swollen cylindrical disks at a rate of 6 mm min^{-1} and a 50 N cell load. Young´s modulus values were recorded between 2–10% strains. Tensile test probes were uniaxially stretched at 60 mm min^{-1} with a 50 N cell load until the probe broke. The fracture toughness was calculated from the area under the stress-strain curves.

Drug loading studies

Dried DAT hydrogel samples were immersed in a solution of imipramine hydrochloride in PBS (2.5 mg/mL) until maximum swelling. The drug that had not been loaded was removed by washing the hydrogels with PBS buffer. The drug loading was then calculated by an indirect method:

$$Drug\ loading\ (\%) = (\frac{m_o - m_u}{m_0}) * 100$$

where m_0 is the total initial mass present in the loading medium and m_u is the mass of the drug that was not loaded. For AM hydrogels, dried samples were loaded with the same amount of IMI/PBS (2.5 mg/ml) as DAT hydrogels. The drug loadings and release profiles were analysed by UV/VIS using a Cary 5000 UV-vis-NIR spectrophotometer. Quantification was performed using calibration curves at the desired wavelength according to the drug studied.

MW (v = 915 MHz) irradiation experiments

All microwave irradiation experiments were carried out using a 915 MHz microwave reactor developed in collaboration with Sairem Ibérica S.L., equipped with a semiconductor generator (5 kW maximum output power, with a 2.5% reflected power) working with progressive waves.

Study of temperature rise with MW exposure

For early experiments at different Incident Powers, P_{inc}, fully swollen cubic-shaped DAT hydrogels (1.5cm × 1.5cm × 1.5 cm approx.) were placed in contact with a Nortech fibre optic thermometer and immersed in 50 mL of PBS in a glass beaker. The beaker was placed inside a waveguide chamber and the chamber was sealed prior to irradiation. The samples were irradiated at increasing incident powers (P_{inc} = 1 kW, 2 kW and 3 kW) and the temperature was monitored every 10" for t_{ir} = 120" for only one MW cycle. Each sample was irradiated in triplicate. Once the curves had been obtained, a temperature-time linear fit was performed. The irradiation times, t_{ir}, at T=38ºC were obtained by interpolation of T = 38 ºC on each curve.

For the study of temperature rise of graphene-based hydrogels, 0.5G-DAT hydrogels were exposed to MW irradiation of P_{inc} = 2kW instead, for t_{ir}= 120". Temperatures were measured every 10" for only one MW cycle.

For the studies at shorter cycles, DAT and G-DAT hydrogels previously loaded with drug were exposed for four MW cycles at P_{inc}= 2 kW for 30"/cycle, for a total time of 3 hours, both in PBS and SGF media After each cycle the samples were allowed to cool to rt (20 ºC) outside the chamber. Temperatures recorded this way were measured during and after each cycle. All measurements were carried out in triplicate.

Study of drug release with MW exposure

For preliminar drug release studies at different Incident Powers, P_{inc}, drug-loaded DAT hydrogels were immersed in 50 mL of PBS solution in a glass beaker inside the waveguide chamber. Hydrogels were then exposed to MW irradiation under different conditions (P_{inc} = 1 kW for t_{ir} = 60" and P_{inc} = 2 kW for t_{ir} = 30") for 4 cycles over 3 h. After each cycle, the beaker was removed from the chamber and 5 mL aliquots were withdrawn from the solutions. Inmediately after, 5 mL of fresh PBS buffer were added to maintain a constant volume and the samples were left to cool to rt, after which they were sealed back inside the chamber. After each cycle the final volume of PBS solution was observed to remain constant, therefore any possible evaporation of the solvent after MW exposure was ruled out. Aliquots were quantified by UV/VIS spectrophotometric analysis by interpolation from calibration curves of drug in buffer solution, following the Lambert–Beer law. Each meassurement was carried out in triplicate.

For 24h experiments, drug-loaded DAT and 0.5G-DAT hydrogels were subjected to MW irradiation of P_{inc}= 2 kW, t_{ir} = 30"/cycle for 4 cycles until 3 h, and left to release until 24 h, both in PBS and SGF media. Similarly, the same experiment was carried out with drug-loaded AM hydrogels under the same MW irradiation conditions Aliquots were analyzed in a similar manner. Each measurement was carried out in duplicate.

SH-SY5Y Cell Culture

Human neuroblastoma SH-SY5Y cells (Sigma-Aldrich) were maintained in Eagle's Minimum Essential Medium (EMEM), supplemented with 10% decomplemented fetal bovine serum, 2 mM L-glutamine, 1 % antibiotics-antimycotics, in a humidified atmosphere supplied with 5 % CO_2 at 37 °C until confluent.

Calcein-AM Viability Assay

Cell viability was assessed using calcein-AM, a nonfluorescent cell permeable derivative of calcein which becomes fluorescent inside living cells. Different hydrogels were lyophilized, (DAT PBS,

DAT SGF, 0.5G-DAT PBS and 0.5G-DAT SGF) cutted into homogeneous slices (approximately 25 mm^2 surface area), transferred to separate wells of a 24-well plate and sterilized by UV illumination from both sides for 10 min. A dilution of $2 \cdot 10^6$ cells/mL in complete medium was prepared and 50 µL of this solution were soaked into each hydrogel. After 20 min of incubation at room temperature, complete medium was added to each well and cells were incubated for 24 h under standard cell culture conditions. The following day, cells were washed with PBST buffer and incubated with 1 µM calcein-AM diluted in complete medium for 15 min at 37 °C. After washing once with PBST, cells were maintained in complete medium until each hydrogel was transferred to a glass slide to visualize green fluorescence.

Confocal Microscopy and image analysis measurements

Images per experimental condition were taken by scanning the hydrogels with confocal microscopy using a Zeiss LSM 800 system (Carl Zeiss, Weimar, Germany). Fluorescent images for each condition were taken as duplicates and acquired using the 10× objective with 1 excitation laser at 494 nm for Calcein-AM (X and Y axes = 638,9 µm). Confocal z slices of around 260 µm were used (from 150 µm to 615 µm) with a 15 µm z interval. Cell counting was done by ImageJ (Fiji, NIH Image)[46] by a blind data collection with Cell Counter plugin..A logistic regression model was used to fit number of cells to the presence of graphene and type of DAT hydrogel (PBS or SGF; SPSS, IBM SPSS Statistics, vs. 24).

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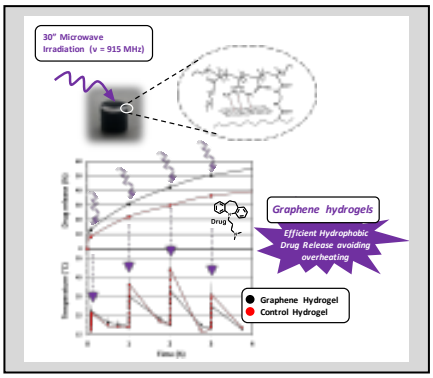

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The first 915 MHz microwave (MW) responsive soft scaffold is herein presented. Long wave 915 MHz microwaves offer several advantages over conventional 2,45 GHz frequencies, such as deep wave penetration and diminished tissue damage associated to MW exposure. The hydrated nature of the scaffold allows MW-induced water motion inside the network to increase mobility of model hydrophobic drug, eventually leading to improved drug delivery. The graphene embedded in the hydrogel matrix acts as a heat-sink during MW exposure and prevents overheating of the scaffold, pointing these hydrogels as suitable candidates for on-demand remote drug delivery. The material can find applications in the biomedical field, such as bioimplants, tissue engineering or 3D cell culture.

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