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Study the Effect of 12-Hydroxyoctadecanoic Acid Concentration on Preparation and Characterization of Floating Organogels using Cinnarizin as Modeling Drug

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Abstract

This work targeted studying organogel as a potential floating system. Organgel has an excellent viscoelastic properties, floating system posses a depot property. Different formulations of 12-hydroxyoctadecanoic acid (HOA) in sesame oil were gelled and selecting F1, F3 and F5 HOA organogels for various examinations: tabletop rheology, optical microscopy, and oscillatory rheology studies. Also, the floating properties studies were conducted at *in vitro* and *in-vivo* levels. Lastly, the *in-vitro* release study using cinnarizine (CN) was to investigate the organogel depot property. Based on the results, the selected concentrations of HOA in sesame oil organogels showed temperature transitions from gel to sol higher than body temperature. These organogels scaffolds inner structures were a star-like shape. The formulation F5 HOA/SO organogels were developing higher storage modulus values, which resulted from the amplitude sweep study. Indeed, all the selected organogels were frequency sweep independent. The organogel's *in vitro* floating properties were found positively proven our work's aim and were buoyant for 24 hours as F5 HOA organogels remained for 12 hours in the rat's stomach. The depot property showed the slow release of CN from F5 HOA/SO organogel and not more than 65% w/w of CN released after 24 hours.

Keywords: Organogel, Floating, Depot, (12-hydroxyoctadecanoic), Sesame oil

دراسة تاثير حمض ١٢-هيدروكسي اوكتاديكانويك على تحضير وتوصيف االهلام العضوي العائم باستخدام السينارizين كنموذج للعقار

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الخلاصة

استهدف هذا العمل دراسة الهلاميات العضوية كنظام عائم يُعرف بالنظام اللزج المطاطي الممتاز والذي يمتلك خاصية المستودع العضوي. تم عمل تراكيز مختلفة من حمض ١٢-هيدروكسي أوكتاديكانويك في زيت السمسم واختيار ثلاث صيغ لفحوصات مختلفة لعلم الريولوجيا المنضدية والفحص المجهري البصري ودراسات الريولوجيا التذبذبية. أيضًا ، كانت دراسات الخصائص العائمة على مستويات في المختبر وداخل الجسم. أخيرًا ، كانت دراسة التحرر الدوائي في المختبر باستخدام دواء السينارizين للتحقيق في خاصية المستودع العضوي. بناءً على النتائج ، أظهرت الصيغ المختارة من ١٢-هيدروكسي أوكتاديكانويك في هلاميات زيت السمسم تحولات درجة الحرارة من هلام إلى سائل او مائع أعلى من درجة حرارة الجسم. كانت الهياكل الداخلية للسقالات العضوية حسب الفحص المجهري نجمية الشكل. كانت صيغ الهلاميات العضوية F5 (١٢ -هيدروكسي أوكتاديكانويك) ذات قيم معاملات تخزين أعلى ، والتي نتجت عن دراسة اكتساح السعة, اضافة الى كون جميع الهلامات العضوية المختارة كانت مستقلة عن اكتساح التردد في دراسة اكتساح التردد. اضافة تم التاكد من خصائص العوم في المختبر للهلاميات العضوية متناسقة مع هدف عملنا وكانت مستمرة لمدة ٢٤ ساعة حيث بقيت F5 (١٢ -هيدروكسي أوكتاديكانويك) من الهلاميات العضوية في معدة الفئران لمدة ١٢ ساعة. أظهرت خاصية المستودع التحرر البطيء لدواء السينارizين من الهلاميات العضوية F5(١٢ -هيدروكسي أوكتاديكانويك) والذي لم يتجاوز ٦٥٪ وزن / وزن (١٢ –هيدروكسي أوكتاديكانويك) بعد ٢٤ ساعة.

الكلمات المفتاحية بالعربي : الهلام العضوي،العائم ، المستودع ، ١٢-هيدروكسي اوكتاديكانويك ، زيت السمسم

Introduction

The major desirable route in drug delivery is the oral route for convenience intake and mastering the oral formulations. However, the following limitations like the low solubility of weakly basic drugs, the inconsistent absorption of some drugs, and the short stay in the stomach affect bioavailability. The gastroretentive systems overcome these limitations by helping keep the drug in the appropriate media of solubility throughout the gastrointestinal tract. Gastroretentive systems are classified as swelling[(1)], mucoadhesive[(2)], high density[(3),] and low-density systems[(4)]; the floating system is a subdivision of low-density system[(5)]. This current study focuses on the low molecular weight organogel to investigate organogel's floating characteristics and depot property. Two studies recently used the organogels of span 40, span 60, and stearic acid to investigate their gastric retention property, and the result showed instant buoyancy and long floating duration [(6, 7)].

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Also, the organogel of HOA/ soybean oil delayed the release of the ibuprofen, and the drug release was indirectly related to the increase of HOA concentration in the organogel. The same outcome of the organogel slow release was shown even in the case of hydrophilic drugs the theophylline and ofloxacin [8, 9]. To explore our aim, cinnarizine (CN) was used as a model drug for its solubility augmentation in the stomach environment and formulated with the organogel of low molecular weight gelator 12-hydroxyoctadecanoic acid (HOA) in sesame oil (SO) to study the organogel's floating and depot properties. This organogel is filled in a hard gelatin capsule for patient intake as a suitable way to deliver the organogel. For the same gastroretintive approach, the hard gelatin capsule was used to load furosemide double-layer film for mucoadhesive and gastroretentive purposes[10]. Furthermore, the use of hard gelatin capsules to deliver organogel for the oral route was in many studies, such as the lecithin in sunflower oil organogel incorporated with metronidazole to obtain a controlled release[11]. In addition, Pereira *et al* was solubilized and loaded in hard gelatin capsules the HOA oragnogel for controlled and slowed release[12].

Material and Methods

Materials

HOA and CN were purchased from Hangzhou Hyper Chemicals China and Baoji Guokang Bio-Technology– China, respectively. The SO was obtained from the local market.

Methods

Preparation of organogel

According to the following concentrations (1%, 3%, 5%, 7%, 10%, 13%, 15%, 18%, 20%) (w/w), the HOA was weighed out then completed the total weight to 1 gm with SO in glass vials. These vials were placed in a water bath at 90℃ for 30 minutes, then let to cool overnight at room temperature. While for drug-loaded organogels, 25 mg of CN was weighed initially; then the HOA was added, followed by SO to reach 1 gm of CN with organogel using the same preparation method. The flow of the organogel content upon inverting the vials correlated with the organogel formation as no flow means successful organogel formation. HOA/SO organogels formulations were assigned and represented in Table 1.

Phase transition (Tabletop rheology)

All the vials of the organogels incubation in a water bath at 90 ºC then the temperature of a water bath was reduced gradually to reach 32 ºC, where the average rate was 2°C/ 15 minutes. At the end of each 15 minutes, the vials were leaning 45° to check organogels status, whether solid or liquid. This phase represents the transition temperatures from liquid to solid for all organogel preparations followed by a reverse-phase by increasing the temperature (2°C/ 15 minutes) to build the transition temperatures from solid to liquid for all organogels.

Table 1. The compositions of the HOA organogels.

Fourmulation number	CN (mg)	HOA% (w/w)	SO % Upto (w/w)
F1	25	1	100
F2	25	3	100
F3	25	5	100
F4	25	7	100
F5	25	10	100
F6	25	13	100
F7	25	15	100
F8	25	18	100
F9	25	20	100

Optical microscopy

Microscopic image preparation was by using an optical microscope and slides. The slides preparation was done by adding a drop of molten organogel on a glass slide while the vials of organogels were stilled set in the water bath at 90°C. A glass coverslip was placed on the top of the gel and flattened softly on the slide. After that, the slide was shifted into the microscope stage to examine and capture images using the software microcapture by the digital microscope camera MC500. The magnification of the microscope was X40.

Fourier transform infrared (FTIR)

FTIR application for selected organogels was by using Shimadzu FTIR-8400S. The spectra recording were from 400 to 4000 cm^{-1}, and the cell plate 201-77160-20 was for oils and KRS-5 for KBr to test solid samples and organogels.

Oscillatory rheology studies

Rheological measurements were carried on Anton par mcr302 rheometer using plate-plate configuration (pp25SN61895) for amplitude sweep test, and frequency sweep test at 25 ºC and the data evaluation was by Rheoplus software. This study was carried out at the University of Petra /Pharmaceutical Center (UPPC).

Amplitude sweep

The amplitude sweep test was applied to identify storage modulus (G'), loss modulus (G"), the linear viscoelastic region (LVER), and the flow point for each preparation. The applied oscillatory strain range was set from 0% to 100% at angular frequency 10 rad s^{-1}.

Frequency sweep

The other oscillatory study was the frequency sweep; the chosen strain was within the range of LVER values obtained from the amplitude sweep study for organogels where the angular frequency changed from 0.1 to 100 rad s^{-1}.

Investigation of the floating properties for organogels

In-vitro floating study

Investigation of the floating parameters was done firstly with an *in-vitro* floating study for the organogel loaded in a capsule. A hot liquid organogel was poured into an empty hard gelatinous capsule's body with the micropipette size 1 gram. The capsule was sealed carefully in a vertical position to be stored in a tube to ensure organogel stability. Then, placing the capsule in a beaker filled with 200 mL of HCl solution pH 1.2, which was already prepared to be at 37°C with a constant stirring at 100 rpm. During this process, visual monitoring the gel status for 24 hours.

In-vivo floating study

This study followed the i*n-vitro* floating to observe *in-vivo* floating property using five healthy adult female Wistar rats weighing 200-210gm. According to the guidelines and approval of the ethical committee of research in the pharmacy college, Mustansiriyah University for animal studies was this procedure. Earlier, those rats reserved was for ten days in plastic cages under standard situations (12 hours of light and dark cycle, 24°C, 35-60% humidity) with free access to their nutrition and water. Then, the rats were abstained from food for 24 hours before running the experiment still water-free access. Methylene blue (0.1% w/w) was added to the selected organogels to discriminate the organogels from the stomach tissues. The ethanol addition was to keep the status of organogel as a liquid to make organogel intake by the rat possible, as ethanol was used in another study to liquefy organogel[13]. Provision one millilitre of the blue liquid preparation was to the rat with an oral gavages tube's aid. These animals were anaesthetized by 50 mg/kg ketamine and 5 mg/kg xylazine intramuscular injection. Then, a cut was made to the abdomen to investigate the floating preparations by the presence of the organogel in the rat's stomach. Photos for stomach were taken at 0 min before administration as a control, then at 1 hour, 2 hours, 6 hours, and 12 hours after giving the organogel.

In-vitro release study

In-vitro release study for CN loaded organogels capsules was accomplished using USP type II apparatus (paddle type). The filled jar was to 900 ml of HCl pH 1.2 that adjusted at 37±0.5°C and 100 rpm. The capsule was positioned into the jars of the apparatus then according to the following time frame (0.083, 0.25, 0.5, 1, 3, 6, 9, 12, 15, 18, 21, and 24) hours; 5 ml was withdrawn from the release media then substituted with equal volumes of fresh medium. Each sample filtration was by a Millipore filter 0.45 μm papers and properly diluted if needed and measured by UV-visible spectrophotometer at 254nm (λ max of CN). Each time point was representative for an average of 3 triplicates and transformed into a concentration using the following equation: y=0.0642x. This equation represents the calibration curve equation resulted from several dilutions of CN in an HCl pH 1.2.

Results and Discussion

Preparation of organogel

All HOA in SO organogels were gelled at 25 ^{0}C and showed no flow after vial inversion, as shown in Figure 1. The gelation concentrations were similar to another study using HOA in canola oil, diacylglycerol oil and unrefined sesame oil[14]. Furthermore, the addition of CN did not disturb the organogel formation. For the subsequent studies, three selected concentrations of organogels (F1, F3 and F5 organogels) were assigned to observe the differences among these organogels.

Figure 1.Inverted vials of HOA in SO at room temperature from left to right the organogel formulations (F1, F2, F3, F4, F5, F6, F7, F8, F9)

Phase transition (Tabletop rheology)

This study was applied to find the temperature that could organogels transfer from one status to another. The selected organogels transition temperatures from sol-gel were from 60ºC to 45ºC, and the reverse transition temperatures of gel-sol within this range (47ºC to 60ºC) as shown in Figure 2. These temperature transitions of all organogel indicated stable formulations in 37 °C the body temperature. Our study's gelation phase range was more stable and different than the HOA in light mineral oil organogel, which showed 20ºC for the 2% w/w of the organogel and 70ºC for the 10% w/w of the organogel[15]. In conclusion, an increase in all selected organogels transitions temperature (sol-gel and gel-sol) as the organogel concentration increased and the transition temperatures were above 37ºC, pointing to a solid status of organogel in the body temperature.

Optical microscopy

This optical microscopy study was applied to probe the morphology of the scaffold that construct the organogels. The study showed, as presented in Figure 3, "star-like aggregates". This pattern showed a remarkable similarity to HOA organogels prepared in a different study in vegetable oil[16]. It was noticed denser spherulites were obtained by increasing the concentration of HOA. In conclusion, The F5 organogel presented the most predictable formula that accomplished the aim of this work compared with the lower concentrations of the organogels as a more connecting scaffold with denser spherulites.

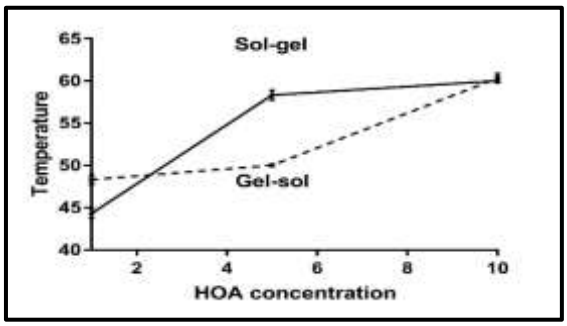

Figure 2. Sol to gel and gel to sol transitions temperatures of selected HOA in SO organogels by vial inversion method.

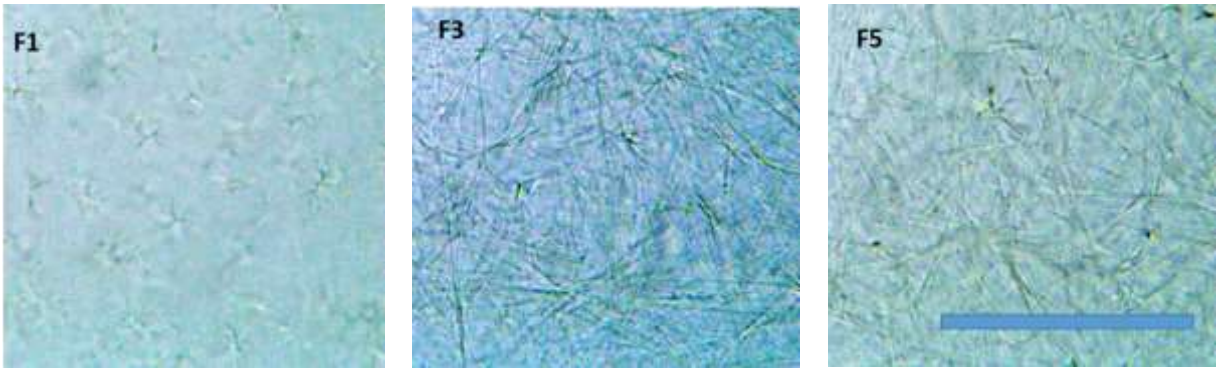

Figure 3. Optical images of selected HOA formulations F1, F3 and F5 in SO organogels as the images taken using X40 magnification and the magnification bar is 50 µm.

Fourier transform infrared (FTIR)

The hydrogen bonds between the functional groups, the carbonyl and the hydroxyl groups of HOA molecules were essential and proved to build the scaffold of organogels usually investigated by FTIR. Hence, the FTIR has been executed; as shown in Figure 4A, the carbonyl associated peaks for selected organogels showed peaks at 1745 cm^{-1} indicating the interactions between SO and HOA molecules. This might indicate the high solubility of HOA in SO. F5 showed a peak at 1698 cm^{-1} which is the exact position of the peak related to the carbonyl group of HOA representing the cyclic dimerization of HOA molecules that help in scaffold constitution[17, 18]. This explicit appearance of carbonyl related peak at 1698 cm^{-1} results from the high content of the HOA.Also, the peaks correlated to hydroxyl groups were almost disappearing in all selected organogels as this means hydrogen bonds between molecules, as shown in Figure 4B.In conclusion, a righteous balance between the interand intra molecularinteraction represented by the gelator-gelator interaction and gelator- solvent interaction

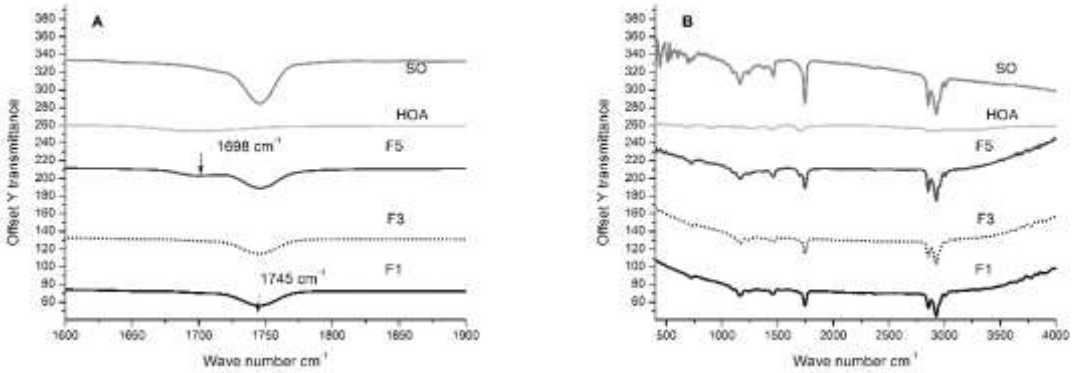

Figure 4. FTIR spectra as the A shows the carbonyl group region, where B displays the whole spectrum.

Oscillatory rheology studies

The dissemination of gels in stomach media reflects their weakness, which is not appropriate for our work that planned to keep the organogels intact to combat the stomach content and motion. Thus, amplitude sweep was applied to test four parameters; firstly, the strength or the elasticity of the organogels via the G' (storage modulus represents the organogel strength or the elasticity), G" (loose modulus represents the viscose status of the organogel). The third parameter is the LVER (linear viscoelastic region signifies the persistence of the organogel elasticity by having an almost constant G' values) and the flow point (means G'=G" and the begun of organogel destruction) as shown in Figure 5 and Table 2. The amplitude sweep figures were Figures 5A, B and C, and it is clear that the G' and G" values were augmented as the HOA concentration increased, whereas the LVER and flow point values showed a reduction. These amplitude sweep study outcomes were similar to span 60 in SO organogels. This effect might be because the increasing spherulite aggregates connections might diminish with gelator concentration augmentation[6].

Table 2 . The amplitude sweep parameters for HOA in SO as each value represent the average of 3 values (n=3) ± SD.

HOA/SO formulation	G' (pa)	G'' (pa)	LVER (%)	Flow point (%)
F1	6329±1954	1117± 443	0.18±0.07	2.4±0.17
F3	95683± 16925	19124± 3838	0.19±0.01	1.4±0.15
F5	442796± 148751	91376± 26634	0.08±0.01	0.96±0.057

G': represents storage modulus and its unit in pascal.
G'': represents loose modulus and its unit in pascal.
LVER: represents the linear viscoelastic region on the G' curve and its unit % as in shear strain.

The frequency sweep execution was to study the motion effect on the organogels, as was shown in Figures 5 D, E and F. All the organogels were frequency-independent as G' and G" were parallel, and G' curves were higher than G" curves. This outcome might point to that the organogels kept their elasticity alongside different frequency values. This result was similar to the organogel of HOA when gelled in soybean oil and medium-chain triglycerides, which showed frequency not depending on organogels[19].

To conclude, the increase in the HOA concentration in the organogel showed an increase in the G' values, reflecting the increase in the solid content. This result harmonized with the conclusion of the organogels image.

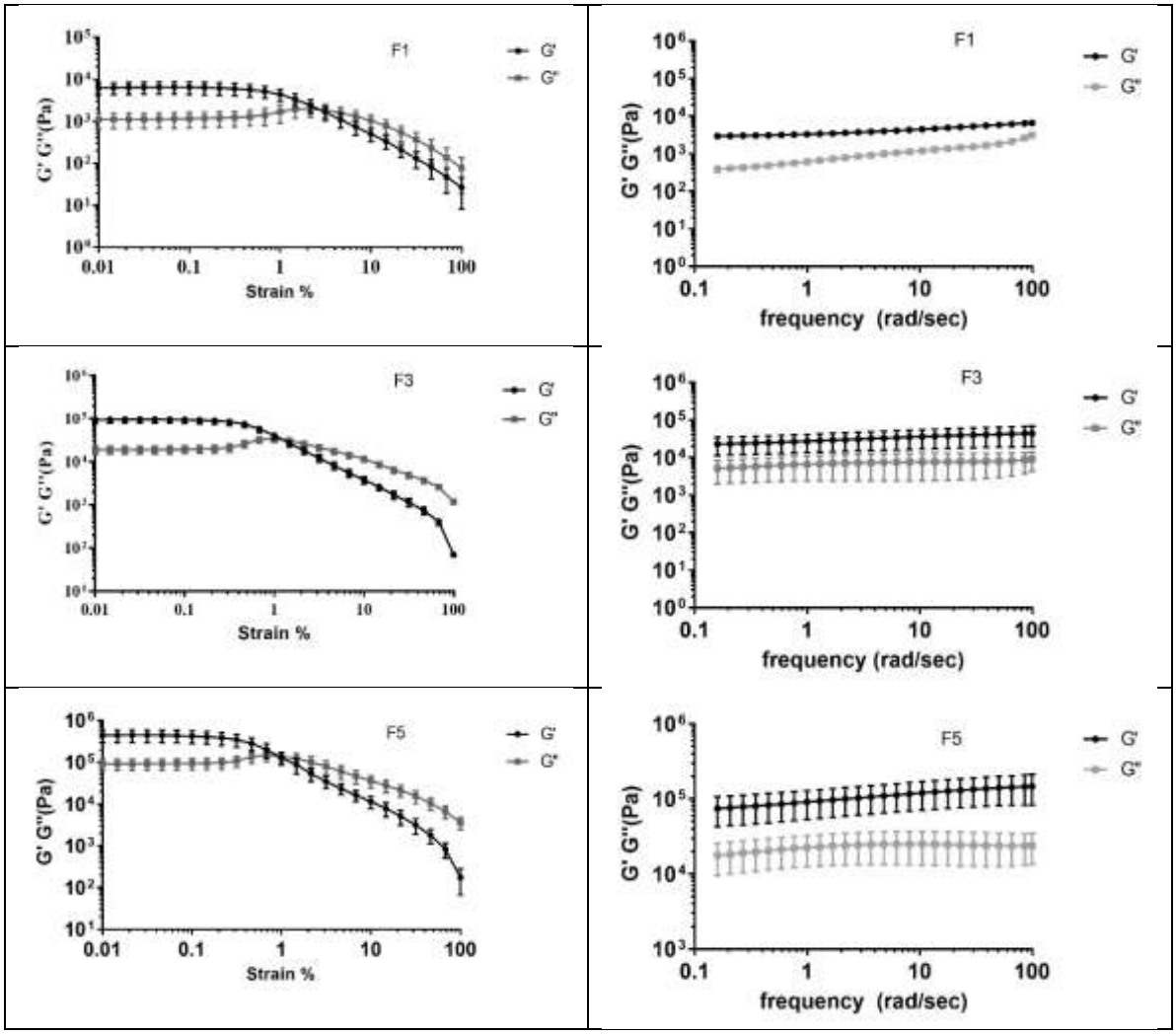

Figure 5. Rheology oscillatory Figures, the A, B and C represent the amplitude sweep, and the Figures D, E, and F represent the frequency sweep of the selected organogels of HOA in SO.

Investigation of the floating properties for organogels

In-vitro floating study

After the organogel gelation in the capsules, the capsules were directly buoyant, and within minutes, the capsule's shells dissolved in HCl media, and the solid organogel was buoyant.

Also, floating duration monitored all the selected HOA organogels and showed the same floating duration of 24 hours. Similarly, oil-entrapped calcium pectinate gel beads float for 24 hours[20]. In a word, all selected organogels were floating for 24 hours.

In-vivo floating study

This study was executed to support the floating *in-vitro* outcomes of HOA organogels. Photos were taken to show the gel formation and it's residues for prolonged periods. The gels were still persistent at the four scarifying times and gradually degraded in the stomach within the time frame, as shown in Figure 6. This result was like the results by AA Aboelwafa *et al* for raft liquid GRDDS that persisted in the rat stomach for 8 hours[21].

As a result, F5 organogel presented the floating and the persisting for 12 hours in the rat's stomach, attaining this study's aim.

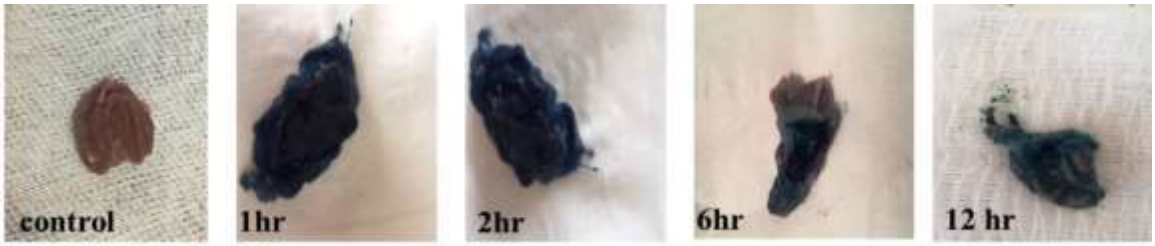

Figure 6: Images showed sectioned rat's stomach at different periods as the F5 organogel was stained with 0.1% w/v methylene blue.

***In-vitro* release study**

The depot property was studied via an *in-vitro* release study using CN that was loaded and solubilized within the selected HOA organogels, as shown in Figure 7. The CN release of F5 and F3 organogels, at 3 hours of the release study was not more than 31% w/w and 41% w/w respectively, and they were barely crossed the 65% w/w and 73% w/w respectively after 24 hours of the study. The F1 HOA oganogels released 69% w/w of CN at 3 hours of experiment, then CN was gradually released, reaching the 100% w/w of CN within the time frame of the release study. Both F3 and F5 HOA organogels emulate in the slowing the CN release the best formulation of the floating tablets that contained carrageenan by Nagarwal group [(22)]. The F5 organogel presented the slowest CN release. This result might be due to the more connecting scaffold as shown in images and the strength presented by the higher values of G' as these might help capture the drugs within the scaffold of the organogel. In summary, the F5 was better in slowing the release of CN than other organogel concentrations.

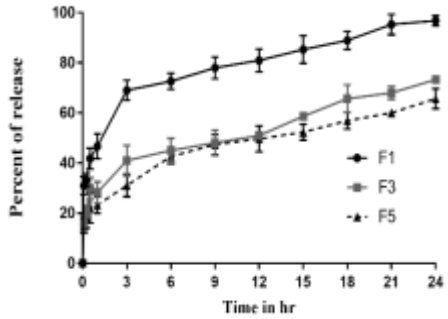

Figure 7. The CN percentage release in stomach solutions pH 1.2 from selected concentrations of HOA/SO organogels.

Conclusion

F5 organogel presented the best values that accomplish the aim of this work compared with the lowest concentrations of the organogels as a more connecting scaffold as shown in microscopy study and higher G' that attributed to the more elastic or strong organogel as well as the slowest CN release for 24 hours. All the organogels were proven to be buoyant by *in-vitro* test for 24 hours, and the floating of F5 HOA/SO was evident in the rat's stomach for 12 hours.

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