Organogel investigations as a floating oral system with depot property

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Abstract:

In this work we investigate span 40, span 60 and SA as a gelators and olive oil (OO) as apolar liquid phase to discover the ability of organogel formed to be floating in acidic media and gain a unique gastroretentive dosage form. In addition, take advantage of the chemical and physical properties of cinnarizine (CN) as a model drug suitable for gastroretentive systems. The floating parameters were studied where the floating lag time and floating duration for organogel in both solid and liquid states. Organogels charecterization were accomplished through the folowing investigatational techniques and analytical methods: table top rheology, optical microscope, Fourier-transform infrared spectroscopy (FTIR) and in-vitro release study. The results showed that all organogels immediately floated and they were floating in both states. Moreover, table top rheology showed that the transition temperature was reversible and higher than 37 ºC except for 7% w/w and 10% w/w SA in OO organogels where, optical images of organogel showed fibrillar network. The FTIR showed peaks associated to carbonyl groups indicated to form gelator-gelator interactions. Moreover, in vitro release study of organogel system showed continuous release CN for 9-12 hours.

Key words: span 40- span 60- stearic acid- olive oil- organogel- gastrortentive dosage form.

تحقيقات في الهلام العضوي كنظام فموي عائم مع خاصية المستودع

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الخلاصة:

تم استكشاف قدرة الهلام العضوي على أن يطفو في الوسط الحمضي والحصول على شكل جرعات معوية باستعمال سبان ٤٠ و سبان ٦٠ و ستيارك اسد كمواد مكونة للهلام و زيت الزيتون كوسط سائل للهلام العضوي. إضافة إلى ذلك ، الاستفادة من الخصائص الكيميائية والفيزيائية لدواء السينارizين لتحضيرها كنظام محتفظ في المعدة. تم تنفيذ حساب مؤشرات المعلمات العائمة وقت بداية العوم و ومدة الطفو للهلام العضوي في كل من الحالة الصلبة والسائلة. بالإضافة إلى عملية دراسة صفات الهلامات العضوية من خلال التحقيقات التالية: علم الجريان على سطح الطاولة والمجهر الضوئي والتحليل الطيفي للأشعة تحت الحمراء و دراسة التحرر في المختبر. أظهرت النتائج أن الطفو كان فوريا في جميع الهلامات العضوية كان صفراً وأنها تطفو في كلتا الحالتين. علاوة على ذلك ، أظهر علم الجريان على سطح الطاولة أن درجة حرارة الانتقال قابلة للانعكاس وأعلى من ٣٧ درجة مئوية باستثناء ٧ ٪ وزن / وزن و ١٠ ٪ وزن / وزن في الهلام العضوي ستيارك اسد في زيت الزيتون حيث أظهرت الصور البصرية للهلام العضوي شبكة ليفية. أظهر التحليل الطيفي للأشعة تحت الحمراء قممًا في المنطقة المتعلقة بمجموعات الكربونيل لتكوين تفاعلات بين المواد مكونة للهلام. علاوة على ذلك ، أدى نظام دراسة التحرر العضوي في المختبر إلى تحرر مديد للدواء و إطلاق مادة سينارizين لمدة ٩-١٢ ساعة.

الكلمات المفتاحية: سبان ٤٠ - سبان ٦٠- ستيارك اسد- زيت زيتون – هلام عضوي - شكل جرعات معوية

Introduction

The advantages of oral dosage form in drug industry are enormous for its uncomplicated manufacturing and more suitable to be taken; though, some difficulties within this type of dosage form are required to be fixed such as: the low solubility of weakly basic drugs, irregular absorption, and short gastric residence time[1, 2]. Gastro retentive drug delivery system (GRDDS) provides an innovative and vital therapeutic choice to resolve these difficulties through improving the solubility and bioavailability of weakly basic drugs and prolonging the gastric residence time. GRDDS classified into: swelling and expanding system, bio/mucoadhesive system, high-density system, and low-density system (floating system)[3]. Recently, floating system is the most popular as it is the most successful and has the fewest side effects of the rest and it subdivided into: effervescent system, hydrodynamically balanced system and raft forming system. Such systems are built with gel forming polymers like chitosan and alginate have been effectively used in many floating drug delivery systems[4, 5].

Alongside, low-molecular weight organic gelators (LMOGs) are favorable candidates to prepare oily gels (oragnogels) since their preparation is uncomplicated and it was reported that they are successful in attaining the sustained release[6].

A range of gelators in this current study were used for organogels preparation as a solid phase. These included: sorbitan monopalmitate (span 40), sorbitanmonostearate, (span 60) and stearic acid (SA). On the other hand, olive oil (OO) was used as a liquid phase.

Spans are lipophilic nonionic surfactants with chemical formulas $C_{22}H_{42}O_6$ and $C_{24}H_{46}O_6$, respectively for span 40 and span 60 and they were commonly used in formulation of vesicles and in emulsion preparation for oral route[7-12]. They were used as LMOGs in organogel for topical preparations such as the study of 20% w/w span 40 organogel in groundnut oil and mustard oil and showed prolonged release of metronidazole[13]. While, 18% w/w span 60 in sunflower oil organogel was used for transdermal application to deliver salicylic acid and revealed a prolonged shelf-life[14]. Also, SA with the chemical formula $C_{18}H_{36}O_2$ and used as a LMOG for oral use in formation of organogel as a core loaded with ciprofloxacin and alginate as a shell forming hybrid microparticles where the *in-vitro* release study exposed the sustained release of ciprofloxacin[15]. For the oral route, span 40 and span 60 were formulated in medium-chain triglyceride organogels that enhanced the solubility of curcuminoids. Furthermore, span 60 prepared as oragnogel with sorbitan monooleate and polysorbate 80 to deliver cyclosporine[16, 17]. Besides OO nutritive benefits and it consist of the fatty acid glycerides, the oleic, the linoleic, and the palmitic acids and it was used as a liquid in organogel via oral route to obtain a depot like effect for lipophilic drugs like ferulic acid where 3% w/w of policosanol in OO was suitable to gain semisolid organogel that showed good properties of organogel and controlled the released of the drug [18].

Cinnarizine (CN) is a muscarinic antagonist, an H1-receptor antagonist and an anti-allergic agent which was chosen as a model drug for its lipophilicity that makes CN suited to be prepared in OO. Also, the weak basicity of CN inspired the scientists to formulate CN for floating system in many GRDDSs[19].

This work was built to connect these findings and the aim was to inspect the floating properties of an organogel prepared from the LMOG that intending for designing a floating system to be delivered in a hard gelatin capsule.

To reach the aim of this work, floating properties of organogel such as floating lag time and floating duration in a solid and as a liquid organogel were investigated. Besides, organogels were explored for their thermal behaviors by table top rheology tester, whereas, the morphological network was examined by optical microscope and FTIR spectroscopy to study the gelators interactions. Additionally, the depot effect of the selected organogels was tested by in-vitro release study of CN in the gastric media at pH 1.2.

Material and methods

Materials

Span 40 and span 60 were purchased from Sinopharm Chemical Reagent Co., Ltd. Also, the followings SA, OO and CN were purchased from AVONCHEM Macclesfied- Cheshire UK Company, the local market (RS Spain) and Baoji Guokang Bio-Technology Co. Ltd –China respectively.

Methods

Organogel preparation

First, organogel without CN was prepared by weighing out a specific amount of each gelator in vials and completing the weight to 1 gm with OO corresponding to the following concentrations of span 40, span 60 and SA in OO (1%, 3%, 5%, 7%, 10%, 13%, 15%, 18%, 20%) (w/w) respectively. All the vials were incubated in a water bath for 40 min at 65°C till a clear solution was attained to confirm the solubility of gelators in oil. Then, the vials were removed from the water bath and allowed to cool at room temperature. These vials were inverted to check the formulation of organogel and when there was no flowing from the organogel preparation the result recorded as a solid organogel. In case of flowing of organogel preparation upon vial inversion, this pointed as a liquid organogel preparation or no gelation.

Second, the CN loaded organogel was prepared as the same above method where the 25mg of CN which was weighed with the selected amount of each gelator, then both components were solubilized in olive oil at 80°C to ensure that the drug dissolves.

Floating properties investigation

The floating parameters for organogels were studied either as a solid organogel filled in a capsule or like a liquefied organogel. Firstly, when the oragnogel is solid filled in a capsule; this process was begun through flowing the warm liquid organogel solution into the body part of the hard-gelatinous capsule (size 00) and then left at room temperature to have a gradual cooling and solidification. Next step is placing the capsule in a beaker filled up to 200 mL with 0.1 N HCl at 37°C with continuous stirring at 100 rpm by magnetic stirrer adjustment.

Second, when the status of organogel was enforced to be as a liquid to ensure that the floating of organogel wasn't related to the ability of hard gelatinous capsule to float; organogel liquefaction was done via adding different concentrations of ethanol to the organogel components in a glass vial where higher concentration of LMOGs required higher concentration of ethanol and then the vial was placed at 65°C in a water bath for few minutes in order to disturb the organogel formation as ethanol breaks the hydrogen bounds among gelator molecules. Then the liquified organogel was injected into a beaker containing 200mL 0.1 N HCl media at 37°C that was rotated at 100 rpm and the change in the status of the organogel from liquid to solid when ethanol escaped to the liquid media was recorded as a gelation time.

The two floating parameters that were performed after preparing the 2 status of organogel are the floating lag time which was the time for both states to start floating and the duration time of permanence organogel floating on the 0.1 N HCl surface which was the second parameter. These parameters were inspected visually

in triplicate along with the gelation time and were characterized as following:
+ = representing a few minutes of gels to solidify, but with quick gel disseminating.
++ = representing instant gelation that continued for just 12 hours.
+++ = representing instant gelation but gels continue for 24 hours.

Table top rheology
All of the organogel vials were incubated in water bath at 80 ºC then the temperature was reduced gradually as 2°C per 15 minutes to reach 32 ºC. At the end of each period of the 15 minutes, the vials were angled for 45° to examine organogels state, whether was solid or liquid. During this process a temperature at which a phase transition from liquid to solid was observed represented the transition temperature for each organogel. The same study was repeated oppositely as a phase went through increasing the temperature at the same rate (2°C/ 15 minutes) to 80°C and the transition temperatures from solid to liquid for all organogels were attained. This study was done in triplicate for each organogel.

Optical microscopy
Microscopic images preparation for organogels started by using slides and optical microscope. The slides were grounded and a melting drop of organogel set on a glass slide directly after taking the vial out of the water bath as the dropping of the liquid organogel was done by a micropipette. Then, a glass coverslip was positioned on the gel with gentle compaction and left for 15 minutes. At that moment, the slide was transported into the microscope stage to examine and capture images by the aid of microscope magnification on X40 and digital camera MC500 accompanied with the software (micro capture).

Fourier transform infrared (FTIR)
FTIR was done for the selected organogels using Shimadzu FTIR-8400S. The spectra range recording was from 400 to 4000 cm^{-1} and the cell plate 201-77160-20 was used for OO and KRS-5 for KBr to test organogels.

In-vitro study
In-vitro release study for CN organogels loaded in capsules was performed by pouring 900 ml of (0.1N HCl, pH 1.2) fluid in the jars of USP type II dissolution apparatus (paddle type) which run at these conditions: 100 rpm and 37±0.5°C. A capsule was located into each jar and the withdrawing process was done according to the following time setting (0.083, 0.25, 0.5, 1, 3, 6, 9, 12, 15, 18, 21 and 24) hours. For each interval, a withdrawal of 5 ml was replaced by 5 ml of fresh medium as each sample was filtered by Millipore filter 0.45 µm membrane. These samples were appropriately diluted and the absorbance was measured by UV-visible spectrophotometer at (254) nm which is CN λ max. The measurement was done in triplicate.

Results
Organogel preparation
The quantitative estimation for the gel forming capacity was by determination the minimum gelling concentration (MGC) which is the minimum concentration of gelator needed for gelation of OO at 25 °C. After organogel preparation in glass vials and they were placed in water bath at 65°C for 40 minutes then air-conditioned them at room temperature, these vials were upturned to test the organogel formation as shown in Figure 1. Span 40 in OO showed gelation at 13%, 15%, 18% and 20% w/w while the lower concentrations were not gelled. Also, the concentrations of organogels of span 60 in OO started at 10% w/w then 13%, 15%, 18% and 20% w/w. Differently, SA in OO was gelled at 5%, 7%, 10%, 13%, 15%, 18% and 20% w/w of SA/OO. The results were in a good agreement with the reported study using span 40 and span 60 in soybean oil organogel where MGC in span 60 was found at 16% w/v and 18% w/v for span

40. However, no gelation was obtained at the lower concentrations in soybean oil[20].

The variances in the MGC for the three different gelators could be related to their different solubility in OO where they were soluble in the oil at high temperature (65°C) at the time of preparation but when they were cooled; they showed variable gelation. This might be as a result of the gelators molecules aggregations on cooling; however, these self - aggregates of gelator was not adequate to form a gel at low concentration of gelators. The assemblies of these aggregates are essential and needed to build up the 3D network structure for the gel formation[21].

In brief, span 40 and span 60 showed MGC in OO at 13% and 10% w/w respectively whereas the MGC of SA in OO was lower than the MGC of spans as it was 5% w/w.

For the next studies, the selection of the organogel concentrations was by choosing three organogels that showed gelation when inverting upside down and these concentrations representing one of the lower, the middle and the higher concentrations. The organogels for span 40, span 60 and SA in OO were (13% w/w, 15% w/w, 20% w/w), (10% w/w, 15% w/w, 20% w/w) and (7% w/w, 10% w/w, 15% w/w) respectively.

Figure (1): Organogels of span 40 as in A, span 60 as in B, and SA as in C. All organogels concentrations were from left to right 1%,3%,5%,7%,10%13%,15%,18%, and 20% w/w and the solid organogel represented as upturned vial.

Floating properties investigation

To investigate floating properties, floating lag time and floating duration should be studied to ensure that the organogels met the aim of the work[22, 23]. These investigations began with organogel as a solid loaded in the capsule.

Lag time: The capsules were instantly buoyant for all preparations and within 5 minutes of the experiment, all capsule shells were melted in 0.1N HCl media and the solid organogel left floating. This result was reported in our work as zero lag time.

The duration of floating: all the selected concentrations of span 40/OO showed identical floating duration which was 14 hours while the selected concentrations of span 60 in OO showed the same floating duration for 10% w/w and 15% w/w which was 20 hours and the 20% w/w floating duration was 24 hours.

The floating duration for 7% w/w SA was 5 minutes, 20 minutes for 10% w/w SA and 20 hours for 15%w/w SA. These parameters were clarified in Table 1 for all organogels.

Certainly, from the above results, increasing the concentration of gelator prolonged the floating duration. This could be because of higher concentration had an increase in the scaffold fiber density which in turn prevent any liquid to penetrate into the scaffold that might help in gel disseminating and sinking, this result is similar to another gastro retentive beads which showed preparation beads with higher concentrations $NaHCO_3$ porogen and $CaCl_2$ as across-linker maintained buoyancy for 20 hours due to denser scaffold obtained[24].

In conclusion, the selected organogels of span 40, span 60 and SA in OO were floating instantly and showed variant floating durations as the higher concentrations exposed the longer durations.

Table (1): The floating duration for solid organogels

LMOG	Oil	(%w/w)	Floating lag time	Floating duration
Span40	OO	13	0	14 hr
		15	0	14 hr
		20	0	14 hr
Span60	OO	10	0	20hr
		15	0	20 hr
		20	0	24 hr
SA	OO	7	0	5 min
		10	0	20 min
		15	0	20 hr

Secondly, to focus on the floating parameters of organogels when they were enforced to be liquids by breaking the hydrogen bounds among the gelator molecules. Table 2 shows the gelation time of liquefied organogels which was recorded in this study. This study was performed to approve the floating properties of the selected organogels with no help from the capsule, as it is well-known that capsule has floating property and it could help our selected organogels to be afloat.

The organogel liquefaction was done by using precise amounts of ethanol to disturb organogel by breaking the hydrogen bounds, the organogels were watched for gelation because the ethanol will leach out once the liquefied organogel poured in any aqueous media. Markedly as shown in Table 2, the selected organogels of span 40 and span 60 in OO showed similar gelation

times 15 min, 12 min and 7 min after using the same volumes of ethanol 100 µl, 150 µl and 200 µl for the minimum, the middle and the highest concentrations organogels, respectively. The same volumes of ethanol were used to the 7% w/w, 10% w/w and 15% w/w of SA in OO and showed gelation times 18 min, 15 min and 10 min respectively. Furthermore, the results of floating properties (lag time and floating duration) similar to those of solid organogels previously studied.

Similar to our wok, the organogel N-lauroyl -L-alanine methyl ester in soybean was liquefied using ethanol where an opaque gel was assembled in the aqueous media within 2 min from pouring [25].

It was evident that, the volume of ethanol used was increased as the concentration of gelator in organogel increased and this could be attributed to increase in the process of self-assembly. This, in sequence, led to increase the volume of ethanol required to dismantle the gelator molecules.

From these results it could be summarized that all, all organogels were liquefied effectively using ethanol and the ethanol volume was increased as the gelators concentration increased in OO but it showed an opposite relationship of gelation time versus concentration of gelators. Besides, all liquefied organogels gelled and showed a similar floating parameter when they were solid in capsules.

Table (2): Gelation time and the floating parameters for liquid organogels

LMOG	Oil	(%w/w)	Ethanol volume (µl)	Gelation time in minutes	floating lag time	Floating duration
Span40	OO	13	100	15	0	14 hr
		15	150	12	0	14 hr
		20	200	7	0	14 hr
Span60	OO	10	100	15	0	20hr
		15	150	12	0	20 hr
		20	200	7	0	24 hr
SA	OO	7	100	18	0	5 min
		10	150	15	0	20 min
		15	200	10	0	20 hr

Table top rheology

Table top rheology is a convenient and simple method to describe phase transitions from solution (sol) to gel and from gel to sol especially for the thermo-reversible organogels, as it is one of organogel characteristics is therm-reversibility.

Phase transition temperatures for organogels from sol to gel and from gel to sol were clarified in Table 3 for the selected concentrations organogels. To start with, sol to gel transitions temperature (Tsol-gel) for the 13% w/w, 15% w/w and 20% w/w span 40/ OO were at 40.33ºC, 41.66ºC and 44ºC respectively.

Amazingly, the MGC of span 60 and span 40 in OO organogels had the same Tsol-gel however, the organogels of 15%w/w and 20% w/w of span 60/OO gelled at 44.16 ºC and 49.66ºC respectively.

Concerning to SA organogels, transition temperature was considerably lower than the previous spans organogels in which the 7% w/w, 10% w/w and 15% w/w of SA/OO gelled at 34.33ºC, 36.33ºC and 40 ºC respectively.

Accordingly, another part of the study has been taken to show the reverse phases of transitions temperature of gel to solution (Tgel-sol) for all organogel preparations.

Starting with span 40/OO organogels, the concentrations 13%w/w, 15% w/w and 20% w/w liquefied at 42.33ºC, 44.33ºC and 46.33ºC respectively. For span 60/OO organogels, Tgel-sol were 42.33ºC, 44.33ºC and 52.33ºC for the concentrations 10% w/w, 15% w/w and 20% w/w, respectively.

Markedly, SA/OO organogels had diverse gel-sol transition temperatures as extended from 34.33ºC, 36.33ºC to 40.33ºC for 7% w/w, 10% w/w, and 15% w/w, respectively.

The above records indicated a direct relationship between the concentration of gelators and the Tsol-gel / Tgel-sol which this might be reasonable because of more fibrous 3D network of organogel when the concentration of gelator increased. These results were recorded in a different study using 2,3-dihydroxycholestane as a LMOG in five different solvents: cyclohexane, dichloromethane, carbon nitrobenzene, aniline and tetrachloride where the transition temperature increased with increasing concentration of 2,3-dihydroxycholestane[26].

Table(3): Transition temperatures of organogels

Oragnogels/OO	LMOGs /Oil (%w/w)	Solution to Gel transition temperature(ºC)	Gel to Solution transition temperature(ºC)
Span40	13	40.33±0.57	42.33±0.57
	15	41.66±0.57	44.33±0.57
	20	44.00±0.00	46.33±0.57
Span60	10	40.33±0.57	42.33±0.57
	15	44.16±0.28	44.33±0.57
	20	49.66±0.57	52.33±0.57
SA	7	34.33±0.57	34.33±0.57
	10	36.33±0.57	36.33±0.57
	15	40.00± 0.00	40.33±0.57

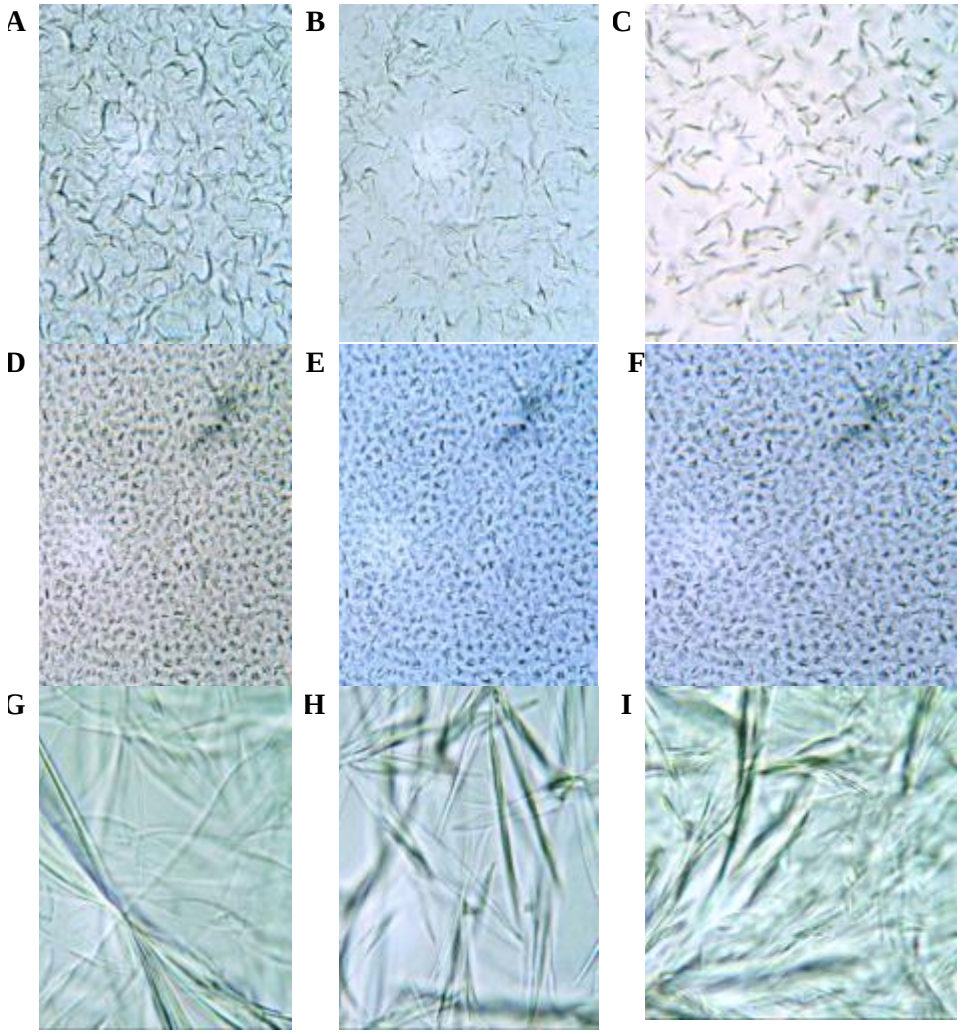
Optical microscopy

This study was performed to examine the morphology cross-section of the organogels scaffold as it was correlated the more connecting scaffold to the slow drug release and previously, a theory by Lam etal related the shortness of fiber to the organogel constitution of highly brunched and connected scaffold. Thus, this study was excuted and the scaffold images are shown for all selected organogels in the Figure 2 as it is recognizable that the three organogels have particular aggregates pattern [27, 28].

Figure 2 A, B and C showed the 13% w/w, 15% w/w and 20% w/w span 40 in OO organogels respectively; they were apparently showed fibrillar networks. This network arrangement is identical to results of study that used span 40 in mustard oil organogel[13]. Likewise, the selected concentrations of span 60 in OO organogels are shown in Figure 2 D, E and F where the organogel network arrangements were fibrillary; even so, they were fibrillar more branched compared to the span 40 organogels. This result in our work is akin to the network arrangements that found by Ibrahim *et al* using light microscope of span 60 in soybean oil organogel[29]. Moreover, Figure 2 G, H and I showed SA in OO organogels and these visually showed shortening in fibers length along with the concentration increasing. This kind of clusters was detected by Schaink *et al* as they prepared 50:50 SA/ stearyl alcohol organogel and these clusters were characterized as feathers[30].

To conclude, all organogels showed a fibrilar network with variable fiber length

for the three gelators where SA recorded as the longest one, followed by span 40 and the shortest one was for span 60.



Figure(2):Microscopic images of span 40, span 60 and SA organogels in which A, B and C representing 13% w/w, 15% w/w and 20% w/w in OO while D, E , and F representing 10% w/w, 15% w/w, 20% w/w in OO and G, H and I representing 7% w/w, 10% w/w, 15% w/w in OO.

Fourier transform infra-red (FTIR)

FTIR spectrum study provides qualitative information and helps to detect the physical interactions among the gelators molecules that are important in gelation and the interactions concerning the components of the organogel.

The highest concentration of the selected organogel alongside gelators (span 40, span 60 SA) and OO spectrogram were studied by FTIR spectroscopy.

First, Figure 3A shows peak at 1747 cm^{-1} that associated with the stretching vibration of carbonyl group of spans 40 in OO organogels spectrograms besides, the OO carbonyl associated peak appeared at an almost similar wave number of the spectrogram. Differently, the carbonyl associated peak of the span 40 spectrogram as a raw material appeared at 1736 cm^{-1}. Nevertheless, Satapathy *et al* prepared span 40 in mustard oil organogel and the change in the carbonyl region were not detected in their FTIR spectrogram[13]. Moreover, Figure 3B focuses on hydroxyl region at 3300 cm^{-1} as these spectrograms

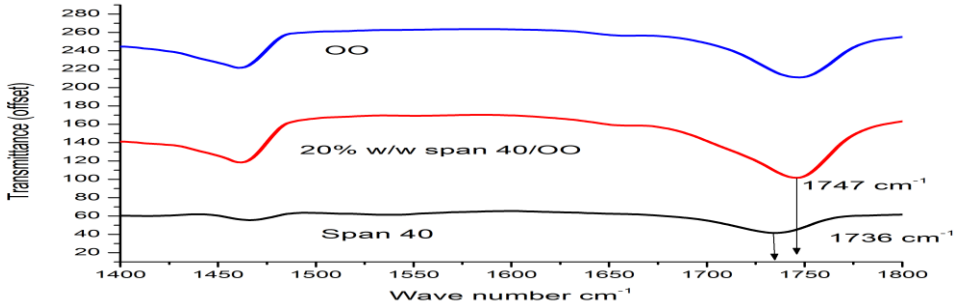
of organogels and showed the small intensity of a broad peak due to O–H stretching comparing with raw span 40 spectrograms. This outcome was like that reported by Behera *et al* as they recognized this change as the intermolecular hydrogen bonding between span 40 molecules that caused gelation in sunflower oil[31].

Second, Figures 3C presents the carbonyl associated region for span 60 and remarkably the findings were similar to span 40 as shown in Figures 3A because the peak shift was from 1736 cm^{-1} of the carbonyl associated peak in span 60 spectrogram to 1746 cm^{-1} in the spectrogram of span 60 organogel while hydroxyl regions in Figure 3D shows a low intensity for the hydroxyl peak. Also, Behera *et al* in another study formulated span 60 in sunflower oil organogel and their FTIR study showed no change in the carbonyl peaks[14]. These shifts in the peaks that are related to the carbonyl group of span 40 and span 60 molecules could be attributed to the intermolecular hydrogen bonds between gelator molecules.

Finally, 15% w/w of SA in OO organogel spectrograms as well the pure SA and OO are presented in Figures 3E and the carbonyl peak region showed an overlapping peak at 1696 cm^{-1} and 1746 cm^{-1} for SA and SA/OO organogels respectively. Another study of SA in sesame oil and soyabean oil organogel showed shifting band at 1710 cm^{-1} of carbonyl which was because of the hydrogen bond formation among the carboxlic groups of gelator[32].

Ultimately, all FTIR spectrograms showed the low intensity peaks associated with the hydroxyl group in span 40 and span 60 organogels indicated that the constitution of organogels, while SA organogel shows overlapping in the carbonyl peak region. The hydrogen bound initiated to form the scaffold by interaction of hydroxyl group of one gelator molecule with the carbonyl group of other gelator molecule to build the 3D network.

A



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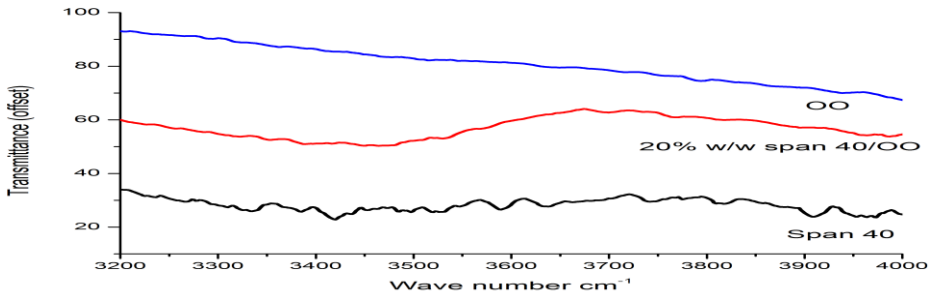


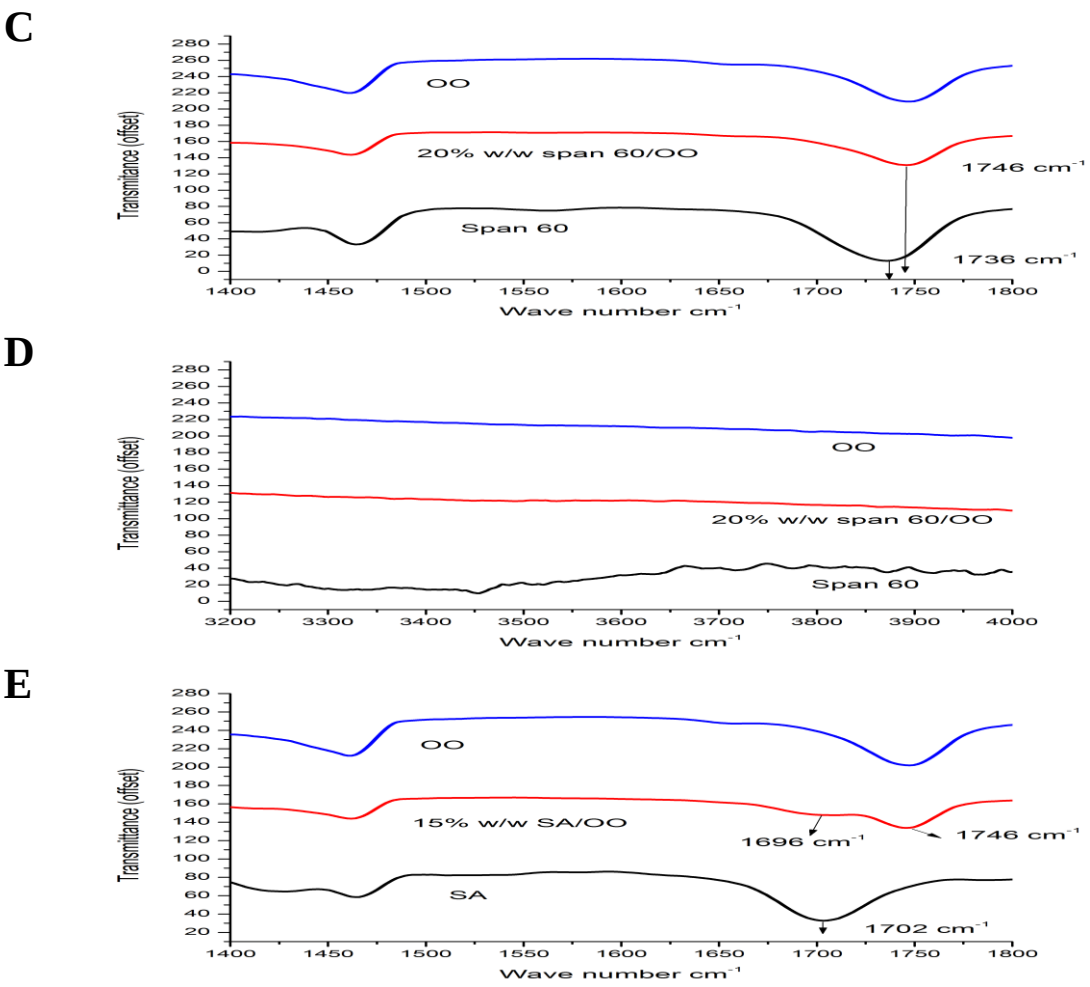


Figure (2): FTIR spectrograms of span 40, span 60 and SA as in A, C and E which represent the region of carbonyl for span 40, span 60 and SA, respectively. B and D represent the spectrogram of hydroxyl region for span 40 and span 60 respectively

In-vitro study

In-vitro CN release study for the three sets of floating system organogel was determined in gastric pH 1.2 for 24 hours to explore the depot property of the organogel.

A control composed of 25 mg CN in OO was run beside the release investigations of organogels to be compared with the organogels. The control was prepared because of the known ability of the oil to hinder the release of hydrophobic drugs. The release profiles of the three gelators and the control formulation were clarified in Figure 4.

It is plain that after 15 minutes of the release study the OO control released 80% w/w of CN and the release of CN was increasing until reaching 100% w/w CN within the frame time of the release study.

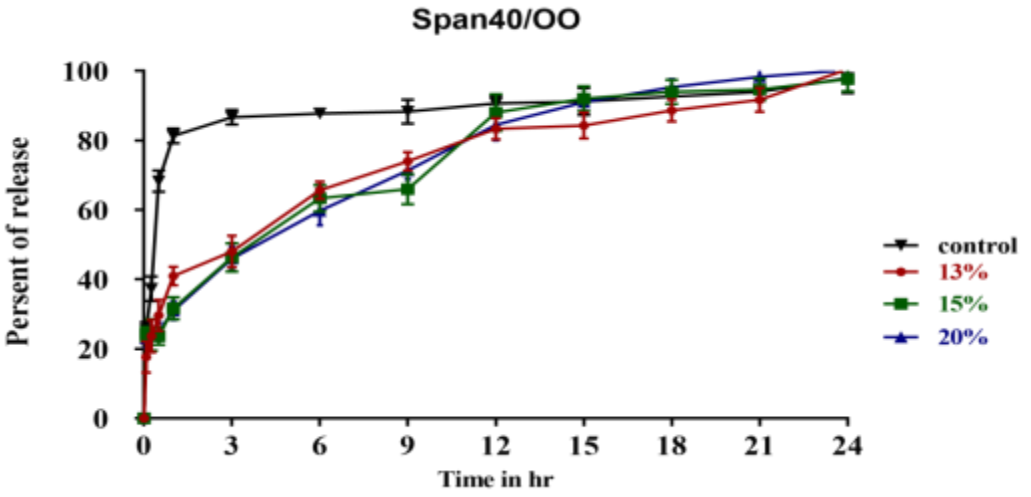
Figure 4A shows the release profiles of selected concentrations of span 40 in OO organogels against control where all the selected organogels of span 40/OO released CN in the similar range irrespective to the concentration of span 40 where at the end of 6 hours 65%w/w, 63%w/w and 59% w/w CN was released from 13% w/w, 15% w/w and 20% w/w span 40/OO organogels while at the end of 12 hours of the release study the same organogels released 83% w/w, 88% w/w and 84% w/w CN respectively. Then, at the end of 24 hours; 100% w/w, 97% w/w and 100% w/w CN was released respectively.

On the other hand, Figure 4 B showed the release of span 60 in OO organogels and presented similar profile as span 40 in OO organogels where 10% w/w, 15% w/w and 20% w/w span 60/OO organogels released CN similarly as the three organogels after 6 hours, 12 hours and 24 hours released CN around 70% w/w, 80% w/w and 95% w/w, respectively.

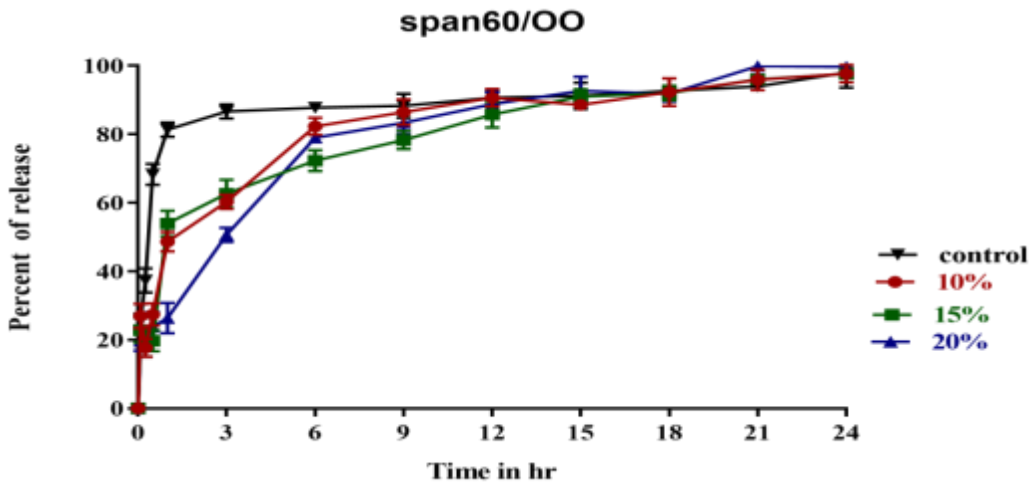
Lastly, Figure 4 C shows the selected SA in OO organogels as the 7% w/w, 10% w/w and 15% w/w SA/OO organogels released 68% w/w, 61% w/w and 59% w/w CN at the end of 6 hours respectively, where at the end of 12hours, 87% w/w, 90% w/w and 72% CN was released. The latest period at 24 hours, 94% w/w, 99% w/w and 77% w/w CN were released, corresponding to the same order of organogels. As shown above, after 12 hours, 15% w/w SA organogel released 72% w/w CN and this percentage of the organogel was close to that CN tablets that were formulated as floating tablet contained sodium alginate and released 75% w/w CN after 12 hours[33].

To sum up, the different concentrations of span 40 and span 60 in the oragnogel had no effect on the release of CN; however, they slowed CN release till the 12 hr of the release study. The same effect was with the SA organogels except the 15% w/w SA/OO organogel slowed the release till the end of the release experiment and showed not more than 77% w/w of CN.

A



B



C

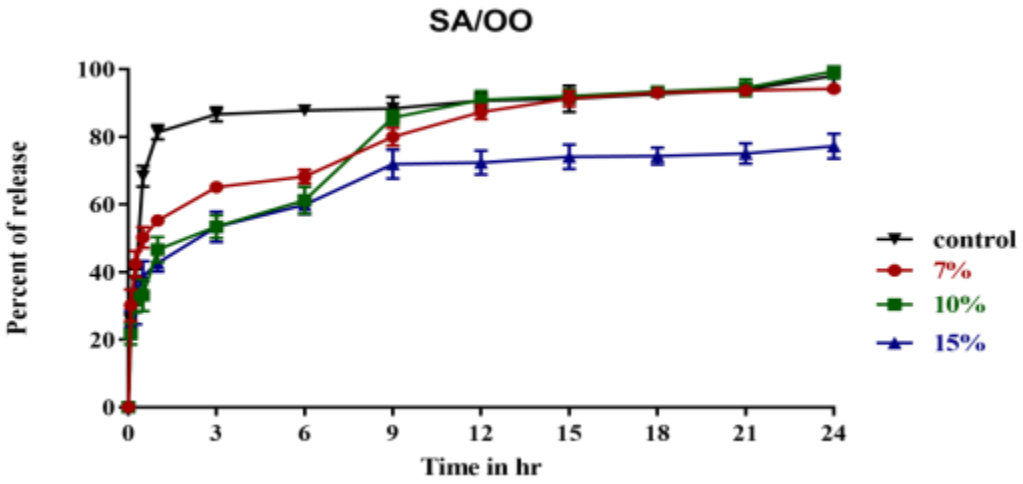


Figure (3): In-vitro CN release where A represents span 40 in OO organogel, B represents span 60 in OO organogel and C represents SA in OO organogel, respectively. The black curve represents the OO control.

Conclusions

The aim of this work was to construct organogel with floating properties and works as a depot to release CN for 24 hours.

Span 40 in OO organogel gelled at 13% w/w and the MGC of span 60 in OO organogel was 10% w/w. In addition, the MGC of SA in OO organogel was 5% w/w. The selected organogels of span 40, span 60 and SA in OO were floating instantly and showed variant floating durations where the higher concentrations showed the longer durations. From tabletop rheology, phase transition temperature for all organogels was reversible and higher than 37 ºC, excepting 7% w/w and 10% SA in OO where they showed transitions temperature for both phases lower than 37 ºC. FTIR showed the interactions of the gelator- gelator to build up the 3D network where the construction of organogels was from the hydroxyl group interaction in span 40 and span 60 while in SA molecules it was from the carbonyl groups interaction. Microscopic images showed the fibrillar network where the fibers lengths were characteristic for each type. In-vitro study showed that all organogels slowed the release of CN against the control for 9-12 hours and the release pattern was comparable for the spans.

From these outcomes it could be concluded that the best organogel obtained is 20% w/w span 40 in OO.

References

1- Lee, Y., et al., Orally disintegrating films focusing on formulation, manufacturing process, and characterization. Journal of Pharmaceutical Investigation, 2017. 47(3): p. 183-201.
2- Mahboob, M.B.H., et al., Oral films: A comprehensive review. International Current Pharmaceutical Journal, 2016. 5(12): p. 111-117.
3- Jassal, M., U. Nautiyal, and J. Kundlas, A review: Gastroretentive drug delivery system (grdds). Indian journal of pharmaceutical and biological research, 2015. 3(01): p. 82-92.
4- Mohamed, M.B.M., et al., Oily in situ gels as an alternative floating platform for ketoconazole release. International Journal of Research in Pharmaceutical Sciences, 2020. 11(2): p. 2638-2649.
5- Pahwa, R., et al., Role of natural polymers in the development of floating drug delivery systems. Journal

of Pharmacy Research, 2010. 3(6): p. 1312-1318.
6- Mohamed, M.B.M., Organogels for intratumoural delivery. 2017, University of Nottingham.
7- Bayindir, Z.S. and N. Yuksel, Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. Journal of pharmaceutical sciences, 2010. 99(4): p. 2049-2060.
8- Toshimitsu, Y. and A.T. Florence, Vesicle (niosome)-in-water-in-oil (v/w/o) emulsions: an in vitro study. International journal of pharmaceutics, 1994. 108(2): p. 117-123.
9- Jadon, P.S., et al., Enhanced oral bioavailability of griseofulvin via niosomes. AAPS pharmscitech, 2009. 10(4): p. 1186.
10- Hasan, A.A., H. Madkor, and S. Wageh, Formulation and evaluation of metformin hydrochloride-loaded niosomes as controlled release drug delivery system. Drug delivery, 2013. 20(3-4): p. 120-126.
11- Sandeep, K., Span-60 niosomal oral suspension of fluconazole: formulation and in vitro evaluation. Asian journal of pharmaceutical research and health care, 2009. 1(2).
12- Wang, L., et al., Design and optimization of a new self-nanoemulsifying drug delivery system. Journal of colloid and interface science, 2009. 330(2): p. 443-448.
13- Satapathy, D., et al., Development of mustard oil-and groundnut oil-based span 40 organogels as matrices for controlled drug delivery. Designed Monomers and Polymers, 2014. 17(6): p. 545-556.
14- Behera, B., et al., Span-60-based organogels as probable matrices for transdermal/topical delivery systems. Journal of applied polymer science, 2012. 125(2): p. 852-863.
15- Sagiri, S.S., et al., Core–shell-type organogel–alginate hybrid microparticles: a controlled delivery vehicle. Chemical Engineering Journal, 2015. 264: p. 134-145.
16- Yu, H., et al., Development of a food-grade organogel with high bioaccessibility and loading of curcuminoids. Food chemistry, 2012. 131(1): p. 48-54.
17- Murdan, S., T. Andrýsek, and D. Son, Novel gels and their dispersions—oral drug delivery systems for ciclosporin. International journal of pharmaceutics, 2005. 300(1-2): p. 113-124.
18- Lupi, F.R., et al., Olive oil/policosanol organogels for nutraceutical and drug delivery purposes. Food & function, 2013. 4(10): p. 1512-1520.
19- Ghareeb, M.M., A.A. Issa, and A.A. Hussein, Preparation and characterization of cinnarizine floating oil entrapped calcium alginate beads. International Journal of Pharmaceutical Sciences and Research, 2012. 3(2): p. 501.
20- MUKHERJEE, S., et al., COMPARATIVE STUDY OF SPAN 40 AND SPAN 60 BASED SOY-GELS FOR TOPICAL DRUG DELIVERY. Asian J Pharm Clin Res, 2019. 12(6): p. 259-265.
21- Alsaab, H., et al., Organogels in drug delivery: a special emphasis on pluronic lecithin organogels. Journal of Pharmacy & Pharmaceutical Sciences, 2016. 19(2): p. 252-273.
22- Getyala, A., et al., Formulation and evaluation of non-effervescent floating tablets of losartan potassium. Current drug delivery, 2013. 10(5): p. 620-629.
23- Devi, P. and V. Rajamanickam, The recent developments on gastric floating drug delivery systems: An overview. Int J Pharm Tech Research, 2010. 2: p. 524-534.
24- Bajpai, S.K. and R. Tankhiwale, Preparation, characterization and preliminary calcium release study of floating sodium alginate/dextran-based hydrogel beads: part I. Polymer international, 2008. 57(1): p. 57-65.

25- Jadhav, N., et al., A REVIEW ON ORGANOGELS: LIPID BASED CARRIER SYSTEMS. Pharma Science Monitor, 2012. 3(4).
26- Edelsztein, V.C., et al., Self-assembly of 2, 3-dihydroxycholestane steroids into supramolecular organogels as a soft template for the in-situ generation of silicate nanomaterials. Beilstein journal of organic chemistry, 2013. 9(1): p. 1826-1836.
27- Sagiri, S., et al., Organogels as matrices for controlled drug delivery: a review on the current state. Soft Materials, 2014. 12(1): p. 47-72.
28- Lam, R., et al., A molecular insight into the nature of crystallographic mismatches in self-assembled fibrillar networks under non-isothermal crystallization conditions. Soft Matter, 2010. 6(2): p. 404-408.
29- Ibrahim, M.M., S.A. Hafez, and M.M. Mahdy, Organogels, hydrogels and bigels as transdermal delivery systems for diltiazem hydrochloride. asian journal of pharmaceutical sciences, 2013. 8(1): p. 48-57.
30- Schaink, H., et al., Crystal network for edible oil organogels: possibilities and limitations of the fatty acid and fatty alcohol systems. Food Research International, 2007. 40(9): p. 1185-1193.
31- Behera, B., et al., Modulating the physical properties of sunflower oil and sorbitan monopalmitate-based organogels. Journal of applied polymer science, 2013. 127(6): p. 4910-4917.
32- Sagiri, S., et al., Stearic acid based oleogels: a study on the molecular, thermal and mechanical properties. Materials Science and Engineering: C, 2015. 48: p. 688-699.
33- Najm, A.S. and W.K. Ali, Preparation and in-Vitro Evaluation of Cinnarizine Raft Forming Chewable Tablets. Al-Mustansiriyah Journal of Pharmaceutical Sciences (AJPS), 2019. 19(3): p. 42-53.