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SPAN 40/TWEEN 80-BASED SOYBEAN OLEOGELS: MODELING OF GELATION KINETICS AND DRUG RELEASE

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Keywords:

Critical gelator concentration, Gelation kinetics, Gel-sol transition temperature, Higuchi model, Organogelator, Surfactant

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ABSTRACT: Background: Oleogel is a thermo-reversible, viscoelastic, semi-solid self-assembled preparation in which an apolar phase gets immobilized within a 3-D networked structure formed *via* physical or chemical interaction with different organogelators. **Objective:** The objective of the present investigation was to develop drug-loaded (paracetamol) Span 40 / Tween 80-based soybean oleogels for topical application and to establish a relationship between viscosity, flexibility, thermal stability and drug release of the oleogels by modeling of gelation and release kinetics. **Method:** Span 40(gelator)/Tween 80(surfactant)-based soybean oleogel formulations were prepared and subjected to organoleptic evaluation, FTIR spectroscopy, thermal analysis, viscosity study, kinetic modeling of gelation and drug release. **Results:** Tween 80 reduced critical gelator concentration (CGC) of Span 40-based oleogels and also enhanced their thermal stability and viscosity. Gelation time was lowered with the increase in concentration of span, but surfactant addition increased the gelation time. Gompertz model was employed on gelation kinetics data for determination of oil parameter (α) and organogelator parameter (β) which were found to be linked to gel flexibility and thermal stability respectively. At lower organogelator/surfactant concentration (16 and 18% w/v), oleogels are assumed to form flexible, less viscous and thermally stable matrix-type oleogel with better drug release. However, at higher organogelator/surfactant concentration (20% w/v), the nearly ideal zero-order release was achieved in contrast to drug release following Korsmeyer-Peppas kinetics from oleogel containing only 20% span. **Conclusion:** Tween 80 is thus assumed to impart higher thermal stability to Span 40 based oleogels probably owing to modification in the microstructure of oleogels.

INTRODUCTION: Oleogels are semi-solid, non-crystalline, non-glassy, thermo-reversible viscoelastic systems, where an apolar phase gets immobilized within the spaces of the three-dimensional networked structure formed due to the physical interactions amongst the self -assembled structures Of organogelators [1]. Sterol, sorbitan monostearate (Span 60), sorbitan mono palmitate (Span 40), lecithin and cholesteryl anthraquinone derivates have been used as organogelators in the development of oleogels [2, 3, 4, 5].

Apolar solvents such as organic solvents (cyclohexane, benzene and carbon tetrachloride), vegetable oils (olive oil, sunflower oil, rice bran oil, seasome oil, *etc*.) and mineral oil have been employed in various studies. Drugs like metronidazole, fluconazole, chlorpheniramine, etodolac *etc*. have been incorporated in previous studies [3, 6, 7, 8]. There are also reports of organogels

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where an aqueous phase has been added to induce gelation [6]. Oleogels are resistant to the effects of moisture and are usually devoid of any aqueous component. Hence, these formulations do not require the addition of stabilizers or preservatives and possess advantages over conventional gels. They are preferable for topical application owing to their ability to interact with skin and also for personal care products like sunscreens, lipsticks, and moisturizers [2]. An ideal oleogel for the topical application would be one with good organoleptic properties, satisfactory extrudability and spreadability, high flexibility, high thermal stability, and improved drug release. It is a common practice to add surfactants such as Tween in development of micro-emulgel, pseudo latex gel for topical, transdermal administration to improve entrapment efficiency, solubility and drug permeation [9, 10]. Therefore, the surfactant may be added in oleogels to obtain better performance.

Span 40 has been used as an organogelator for preparation of organogels of olive, mustard and groundnut oil [3, 4]. No attempt has been made in the past to utilize Span 40 as organogelator for soybean oleogels. Soybean oil contains linoleic acid, isoflavones, anti-oxidants and vitamins that provide nourishment to the skin and soybean oil containing gels and lotions reportedly protect our skin from UVB rays, free radical-induced inflammation, reduce transdermal water loss on the skin and promote skin barrier recovery [11]. Tween 80 has been used as a surfactant for Span 60 and Span 80-based oleogels. In case of Span 80-based formulations, water has been added to form a gelled structure [6].

In the present study, Span 40 has been selected as organogelator for gelation of soybean oil. The investigation focussed on adding Tween 80 as a surfactant to modify the micro-architecture of Span 40-based oleogels devoid of an aqueous phase. The objective of the present study was to develop drug-loaded Span 40 / Tween 80-based soybean oleogels for topical application and to establish a relationship between viscosity, flexibility, thermal stability and drug release of the oleogels by modeling of gelation and release kinetics.

MATERIALS AND METHODS:

Materials: Soybean oil (Emami Ltd., Kolkata) was procured from the local market, Kolkata, West Bengal. Span 40 and Tween 80 were of AR grade and obtained from Loba Chemie and Merck Specialities Pvt. Ltd respectively and paracetamol IP (PCM) was received as a gift sample from the enlisted vendor.

Methods:

Preparation of Oleogel: Accurately weighed Span 40, paracetamol (2%w/w for drug-loaded batches) and Tween 80 was dissolved in soybean oil, maintained at 60ºC with continuous stirring in mechanical stirrer (REMI) at 500 r.p.m for 1h after which a clear, homogeneous solution was obtained. Subsequent cooling down to room temperature (25ºC) formed an oleogel on gelation. The formulations were stored in glass vials and considered to be gel if they did not flow on inversion. Oleogels were prepared by varying concentration of gelator with or without the addition of surfactant according to the composition given in **Table 1**.

TABLE 1: COMPOSITION OF OLEOGEL*

Batch	Composition (%w/v)			
	Span 40	Tween 80	Soybean oil	PCM
OG 1	16	-	82	2
OG 2	8	8	82	2
OG 3	5.33	10.67	82	2
OG 4	10.67	5.33	82	2
OG 5	18	-	80	2
OG 6	9	9	80	2
OG 7	6	12	80	2
OG 8	12	6	80	2
OG 9	20	-	78	2
OG10	10	10	78	2
OG 11	6.67	13.33	78	2
OG 12	13.33	6.67	78	2

*OG 4′, OG 5′, OG 8′, OG 9′ and OG 12′ are corresponding blank gels (PCM absent) of OG 4, OG 5, OG 8, OG 9 and OG 12.

Evaluation of Oleogels:

Fourier Transform Infrared (FT-IR) Spectroscopy: Infrared spectroscopy of raw materials, blank, and drug-loaded oleogels were scanned by using FT-IR spectroscopy (Bruker, Alpha-T) in attenuated total reflectance (ATR) mode in the range of 4000-500 cm^{-1}.

Organoleptic Evaluation: The freshly prepared formulations were subjected to organoleptic evaluation for their color, odor, opacity, and appearance.

Extrudability: Extrusion of oleogel was studied by filling the formulation in a collapsible tube by measuring the distance traveled by the ribbon of gel in 10 sec. Extrudability is expressed as cm/s.

Spreadability Study: [4] Approximately 1 g of the oleogel was placed between two glass slides of equal weight, area, and thickness. Initial spreading diameter (D_i) was noted. After that, a load of a known weight of 10, 20, 50, or 100 g was applied individually on the upper slide for 1min, and the final spreading diameter (D_f) of the gel was noted in each case. The % spreadability was calculated as per the equation is given below.

$$\% \text{ Spreadability} = [(D_f - D_i)/D_i] \times 100 \ldots\ldots\ldots\ldots\ldots (1)$$

pH Measurement: The pH was measured by immersing the glass electrode of the digital pH meter (Eutech Instruments pH Tutor) in the prepared oleogel.

Drug Content Study: [12] The paracetamol content in oleogels was determined as per the pharmacopoeial procedure.

Thermal Analysis:

A) Gelation Kinetics: Gelation kinetics was performed by nepheloturbidometry ((ELICO® CL 52D). Oleogel in sol state was transferred to Nessler cylinder. When the light passes through the sample having turbidity, light is scattered by the suspended particles. The scattering of light is proportional to the turbidity. Turbidity was measured at 20-sec interval from the amount of light scattered by the sample and intensity of turbidity is expressed in terms of nepheloturbidity unit (NTU). Transformation of sol to gel was characterized by an increase in turbidity which continued for a certain period after which there was no further increase in turbidity. The time at which turbidity attained a constant value is defined as gelation time.

B) Gelation Kinetics Modelling: [13] Gompertz model was employed for modeling of gelation kinetics. This non-linear model indicates a relationship between turbidity intensity (NTU), the concentration of gelator or gelator-surfactant in % w/v (ρ) and time for gelation in h (x).

α is defined as the non-polar solvent(oil) parameter whereas β indicates organogelator parameter:

$$\text{Log } Y = \alpha + \beta\rho^x \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

In the above equation, ρ^x is defined as:

$$\rho^x = \rho_1^x + \rho_2^x + \rho_3^x + \ldots\ldots \quad (3)$$

Where, ρ_1 indicates organogelator concentration, ρ_2 indicates surfactant concentration; ρ_3 indicates other additive concentration and so on.

C) Determination of Gel-Sol Transition Temperature (T_g): [3] Thermal analysis of oleogel was done by a drop ball method for determination of the gel-sol transition temperature (T_g). A stainless steel ball having the diameter of $1/8^{th}$ inch and a weight of 230 mg was placed over the formulation in a beaker and attached with a melting point apparatus (EI-931). The formulation was heated at a rate of 1 ºC/min. The temperature at which the ball started to move into the gel was noted and considered as the gel-sol transition temperature of gel (T_g).

Viscosity: Viscosities of all prepared formulations were determined by using a Brookfield digital viscometer (Model LVDVI+) at 25 ºC. The study was done by applying a shear rate of 1 rpm (spindle 6) for 1 min.

***In-vitro* Drug Release Study:** [12] Modified Franz diffusion cell was used to perform the in vitro drug release study on prepared oleogels through dialysis membrane-60 (HIMEDIA® LA 330-5MT). Accurately weighed drug-loaded oleogel containing PCM equivalent to 4mg of the drug was placed on the membrane and wetted slightly with phosphate buffer (pH 5.8). The buffer solution in the receptor compartment was maintained at 32 ± 0.5 ºC.

An aliquot of 1 ml was withdrawn every hour for 7h and replenished with fresh buffer. Following appropriate dilution, an aliquot was analyzed by UV–visible spectrophotometer (UV 1800 UV-vis spectrophotometer, Shimadzu Corporation) at a wavelength of 249 nm.

Hemocompatibility Study: [14] Accurately weighed (1g) oleogel was placed inside dialysis tubing, immersed in 50 ml of normal saline and incubated at 37°C for 1 h in a shaker incubator to allow the leaching of the components from the oleogels. A small volume (0.5 ml) of the leachant was then diluted with 0.5 ml of diluted goat blood (prepared by diluting 8 ml of fresh goat blood with 10 ml of normal saline) followed by the addition of 9 ml of normal saline. The mixture was then incubated at 37 °C for 1 h followed by centrifugation at 3000 rpm for 10 min. Positive and negative controls were also prepared by using 0.1 N hydrochloric acid and normal saline in place of the leachant respectively. The supernatant was analyzed at 545 nm using UV-visible spectrophotometry. The test measures the extent of hemolysis in the presence of the oleogel. Percent hemolysis is calculated by the formula.

$$\% \text{ Hemocompatibility} = (OD_{test} - OD_{negative}) / (OD_{positive} - OD_{negative}) \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

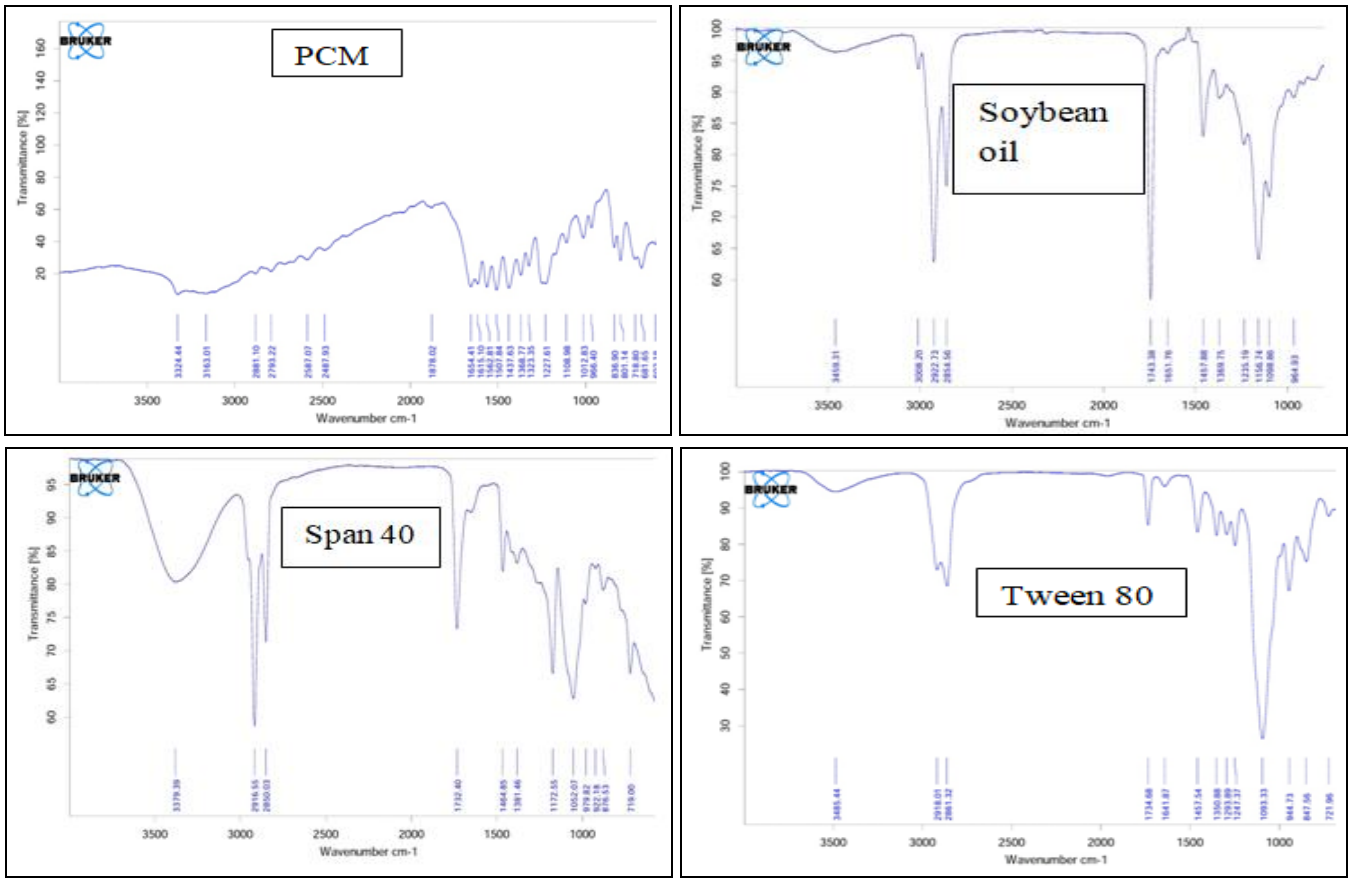
Where, OD_{test} = optical density of test sample, $OD_{negative}$ = optical density of negative control, $OD_{positive}$ = optical density of positive control.

Statistical Analysis: Data have been obtained from each experiment in triplicate (n=3) and were subjected to statistical analysis using one-way analysis of variance (ANOVA). Results are quoted as significant where $p<0.05$.

RESULTS:

Oleogel Formation: The minimum gelator concentration at which the gelation is induced is considered as the critical gelator concentration (CGC) [4]. The CGC of soybean oil-based oleogel was found to be 18%w/v for Span 40 oleogel (OG 5) and 16% w/v for oleogel (OG 4) containing Span: Tween in the ratio of 2:1.

FT-IR Spectroscopy: FT-IR study was performed for Span 40, Tween 80, soybean oil, PCM, drug-loaded and its corresponding blank oleogel (OG 9 and OG 9′ respectively) and similarly for oleogels containing Tween 80 (OG 12 and OG 12′) **Fig. 1**.



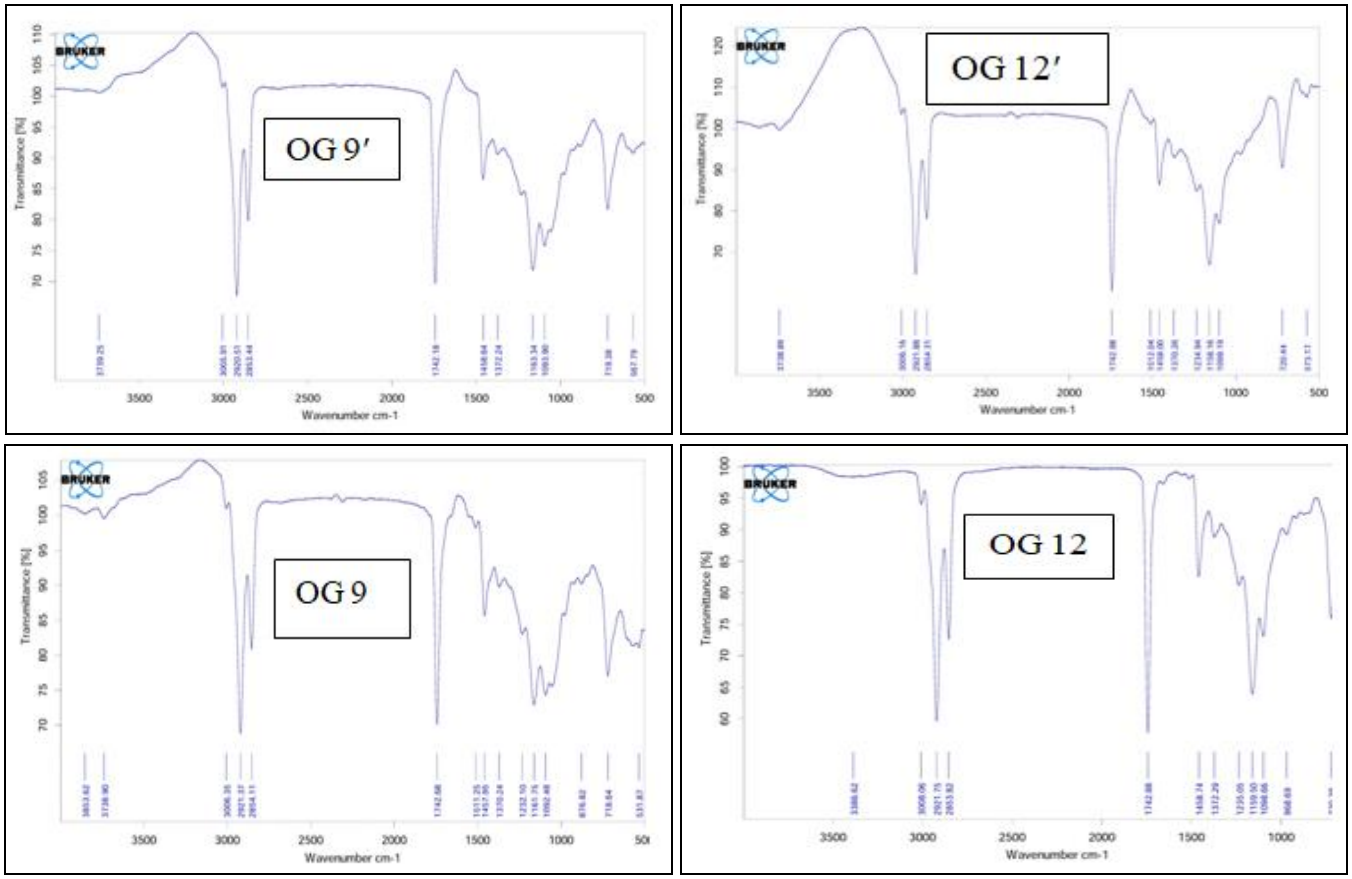


FIG. 1: FT-IR SPECTRA OF OLEOGELS AND THEIR CORRESPONDING BLANK GELS ALONG WITH RAW MATERIALS

Peaks at 2913, 2855, 1744, 1157 and 719 cm^{-1} were found in the spectrum of soybean oil. Most of the characteristic peaks of Span 40, soybean oil and drug were visible in the blank (OG 9′ and OG 12′) and drug-loaded oleogels (OG 9 and OG 12). Similarly, peaks of Tween 80 could be detected in a formulation containing the surfactant (OG 12 and OG 12′). FT-IR spectral analysis of Span 40 revealed a broad peak at 3300 cm^{-1} indicating the presence of O–H stretching vibrations [4].

Organoleptic Properties: The organoleptic properties of prepared oleogels are summarized in **Table 2**. OG 5 and OG 9 were found to be yellowish-white in color, odorless and opaque, but after addition of Tween 80, the gels became transparent and acquired yellow color (OG 4, OG 8 and OG 12). All the samples were smooth-oily in touch.

Extrudability and Spreadability Study: All the prepared formulations were homogenous, uniformly dispersed and extruded properly from the collapsible tube **Table 2** and did not lose their structural integrity after the application of load in spreadability test. The % spreadability of prepared oleogels on application of different weights is graphically represented **Fig. 2**.

pH Measurement: All the prepared formulations were compatible with skin pH (5.5 ± 0.3) at 25 ºC.

Drug Content: The drug content of oleogels was found to be in the range of 97-98% **Table 3**.

TABLE 2: EVALUATION OF ORGANOLEPTIC PROPERTIES AND EXTRUDIBILITY DETERMINATION OF OLEOGEL

Batch	Organoleptic Characteristic				Extrudability (cm/s)
	Colour	Odor	Opacity	Appearance	
OG 4	Yellow	Odorless	Transparent	Smooth-oily	1.2 ± 0.5
OG 5	Yellowish-white	Odourless	Opaque	Smooth-oily	0.8 ± 0.6
OG 8	Yellow	Odorless	Transparent	Smooth-oily	1.1 ± 0.4
OG 9	Yellowish-white	Odorless	Opaque	Smooth-oily	0.7 ± 0.5
OG 12	Yellow	Odorless	Transparent	Smooth-oily	1.0 ± 0.3

TABLE 3: DETERMINATION OF DRUG CONTENT, GEL-SOL TRANSITION TEMPERATURE (T_g), VISCOSITY AND HEMOCOMPATIBILITY OF OLEOGELS

Batch	Drug content (%)	T_g (ºC)	Viscosity (cPs) at 25 ºC	Hemocompatibility
OG 4	97 ± 0.1	49 ± 0.2		Pass
OG4′			3.03×10^4	
OG 5	98 ± 0.2	42 ± 0.1		Pass
OG 5′			3.9×10^4	
OG 8	97 ± 0.2	51 ± 0.2		Pass
OG 8′			9.47×10^4	
OG 9	98 ± 0.3	46 ± 0.3		Pass
OG 9′			4.43×10^4	
OG 12	98 ± 0.2	51.5 ± 0.2		Pass
OG 12′			1.203×10^5	

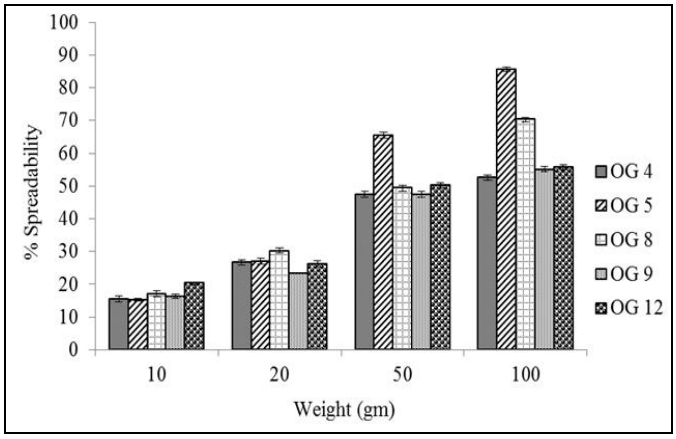


FIG. 2: CHANGE IN % SPREADABILITY WITH APPLICATION OF LOAD (G) ON OLEOGELS. Error bars represent standard deviations for 3 experiments.

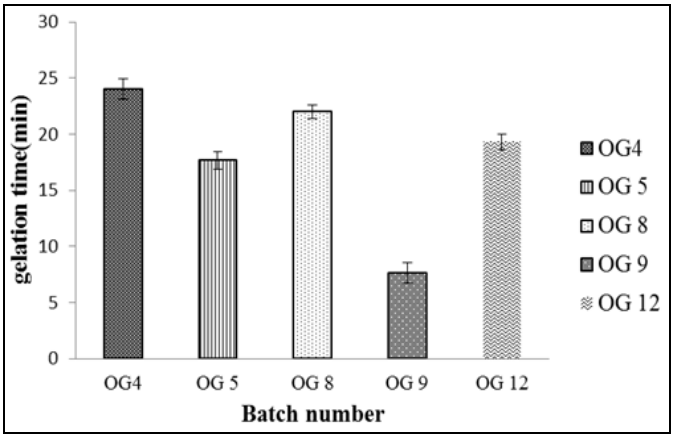


FIG. 3: CHANGE IN GELATION TIME WITH CONCENTRATION OF GELATOR AND GELATOR/ SURFACTANT. Error bars represent standard deviations for 3 experiments.

Modeling of Gelation Kinetics: The gelation kinetics was studied by monitoring the change in turbidity during cooling of the oleogels in a liquid state. The change of gelation time with gelator/ surfactant concentration is shown graphically in **Fig. 3**. Gel-sol transition temperature (Tg) of the formulations is presented in **Table 3**. Gompertz model was employed for modeling of gelation kinetics to determine oil parameter (α) and organogelator-surfactant parameter (β) **Table 4** which are related to gel flexibility and thermal stability of the oleogel respectively.

TABLE 4: MODELLING OF GELATION KINETICS OF OLEOGELS

Batch	Gompertz model	
	α	β
OG 4	2.5708	0.1799
OG 5	2.0726	0.5791
OG 8	2.2059	0.2715
OG 9	2.062	0.8454
OG 12	2.1347	0.2979

Viscosity: The prepared oleogels can be ranked in the following order concerning the observed viscosity values **Table 3** as OG 12>OG 8>OG 5 > OG 9>OG 4. After surfactant addition, the viscosity increased.

***In-vitro* Drug Release Study:** The drug release profile of PCM from the prepared oleogels has been shown in figure **Fig. 4**. The percentage of drug release decreased with increase in Span 40 concentration, but surfactant addition improved release from oleogels. Kinetic modeling of drug release was studied and tabulated in **Table 5**.

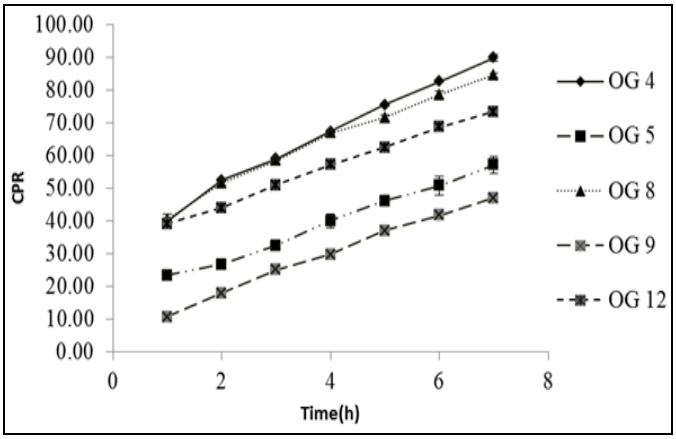


FIG. 4: DRUG RELEASE PROFILE FROM OLEOGELS. Error bars represent standard deviations for 3 experiments.

TABLE 5: MODELLING OF DRUG RELEASE KINETICS

Batch	Kinetic followed	R^2	n
OG 4	Higuchi	0.9939	0.4103
OG 5	Zero	0.9943	0.5
OG 8	Higuchi	0.9972	0.3748
OG 9	Korsmeyer-Peppas	0.999	0.7629
OG 12	Zero	0.9981	0.3316

Hemocompatibility Study: All the formulations were found to be hemocompatible as the observed hemolysis was <5% [14].

DISCUSSION: Change in the solubility parameter of Span 40 molecules with lowering of temperature resulted in decreased affinities between oil and Span causing self-assembly of Span molecules into aggregates [3]. A three-dimensional network might have been formed by joining of several such aggregates thereby capturing the oil molecules within. It has been observed that the addition of Tween resulted in the formation of a clear, transparent solution at 60 ºC initially. This might be due to the ability of Tween to improve the solubility of Span in soybean oil *via* the formation of mixed inverse micelles. Moreover, surfactant addition was found to induce gelation slowly but at a lower concentration of Span 40. It seems that Tween promotes aggregate-aggregate interactions which are stronger than solvent-aggregate affinities, leading to gel formation [15].

FTIR analysis of the oleogels revealed slight shifting in the peaks of the individual components as well as minor changes in peak intensity indicating compatibility between the oil, organogelator, surfactant, and drug. Absence of the broad peak at 3300 cm^{-1} in oleogels with or without surfactant may be attributed to inter-molecular hydrogen bonding amongst the fatty acyl groups of gelator and oil molecules, which is responsible for imparting strength to the gels [16, 17]. Minor variations were observed in organoleptic properties and drug content of the different oleogel formulations. The oleogel formulations demonstrated satisfactory extrudability, spreadability and skin-compatible pH indicating their suitability for topical application.

Thermal analysis of oleogels suggested that increase in gelator concentration decreased gelation time and caused the gel to sol transformation to occur at a higher temperature. In contrast, the addition of Tween increased the gelation time and formed gels with higher Tgs. The Tg values of most of the formulations were higher than the melting point of Span 40 except for OG 5 and OG 9 containing only Span. The increase of Tg with the increase in gelator concentration and surfactant addition indicate that self-assembly in the gel state is governed by strong intermolecular interactions attributable to Span 40 or inter-aggregate interactions in case of Tween 80. [18] It is to be noted that gel microstructure might have been influenced by Tween 80; leading to better gel stability [15]. The transformation process is reversible as the gels reformed on cooling exhibiting same properties as before [15].

Oleogels containing Tween (OG 4, OG 8 and OG 12) were found to possess higher α- value compared to corresponding Span-based oleogels indicating higher flexibility. However, they were found to possess higher viscosity than Span-based formulations except OG 4 suggesting the propensity of Tween to undergo physical interactions and form flexible (higher α- value) but the compact mesh-like self-assembled structure within the gels. Lower β-value and simultaneously higher Tg for the same formulations indicate better thermal stability of the gels. Therefore, it can be inferred that Tween 80 reduces CGC of Span 40-based oleogels, imparts higher thermal stability to oleogels at lower β-value and can presumably modify the microarchitecture of oleogels. The gels with higher α value and low viscosity are expected to demonstrate improved drug release from oleogels owing to higher gel flexibility. As the concentration of gelator was increased, α-value decreased indicating the formation of comparatively rigid gels with higher viscosity (OG 9> OG 5) and better thermal stability as manifested in increasing β-value and higher Tg.

Release of PCM from oleogels depends upon the solubility and partition coefficient of the PCM in soybean oil [6]. Improved drug release from oleogels containing Tween (OG 4, OG 8 and OG 12) is attributed to the flexible gel network as evident from the thermal analysis. Similarly, lower organogelator concentration in OG 5 accounts for higher drug release compared to OG 9. It has been reported earlier that the release of the drug molecules from mustard oil and ground nut oil based organogels decreased with increase in gelator

concentration due to the formation of dense networked structures that hinder the diffusion of the drug molecules [4]. It was found that OG 5 followed zero order release kinetics with Fickian diffusion, but drug release from OG 9 occurred *via* non-Fickian diffusion and followed Korsmeyer-Peppas model. OG 4 and OG 8 are assumed to form a planar homogenous gel matrix with no loss of structural integrity as drug release followed Higuchi model [3]. In the case of OG 12 containing 20% organogelator/ surfactant (Span: Tween in the ratio of 2: 1), there was a transformation of release kinetics from Korsmeyer-Peppas to zero-order. Combining the results from the above studies, it can be concluded that addition of 16% organogelator / surfactant (Span 40: Tween 80 = 2 :1) produced most flexible matrix-type oleogel with least viscosity and high gel-sol transition temperature from which drug release improved remarkably.

CONCLUSION: Thus, from the above studies it can be concluded that Tween 80 plays a crucial role in inducing gelation of soybean oil at a lower concentration of Span 40 and forming flexible oleogels of improved thermal stability and better drug release compared to oleogels containing only Span. For formulations containing Span/Tween, at lower organogelator/surfactant concentration (16 and 18% w/v), oleogels are assumed to form a matrix. However, at higher organogelator/ surfactant concentration (20% w/v), the nearly ideal zero-order release was achieved.

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CONFLICT OF INTEREST: Nil

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