COMPARATIVE STUDY OF SPAN 40 AND SPAN 60 BASED SOY-GELS FOR TOPICAL DRUG DELIVERY

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Received: 11 April 2019, Revised and Accepted: 01 May 2019

INTRODUCTION

Gels are suitable dosage forms for topical application due to their ease of manufacturing, excellent appearance, smoothness, desired consistency, convenience in handling, superior drug release profile, and finally affordability. They are composed of polymeric gelating component forming a closely entangled mesh of aggregates by immobilizing the liquid component [1]. Gels may be categorized as a hydrogel, emulgel, organogel or oleogel depending on the polarity of the liquid component [2]. Hydrogels are three-dimensional (3D), hydrophilic, polymeric networks capable of imbibing large amounts of water, or biological fluids [3]. However, they are highly susceptible to microbial contamination and also possess poor mechanical strength [4]. On the other hand, absorption of macromolecules from emulgels is low and bubble formation may occur during emulgel formulation [5].

Recently, attempts are being made to modify gel formulation by developing organogel which is a gelled homogenous mixture of non-ionic surfactant with a non-polar organic solvent or vegetable oil at room temperature [6]. Organogels is a thermodynamically stable, viscoelastic system comprising of a gelator (any substance capable of forming gel) and a nonpolar phase (non-aqueous), with or without the presence of water molecules within the network formed by the gelator system [7]. Drug molecule may be incorporated either in the organic phase or sometimes in the aqueous component.

Gelators are organic molecules capable of gelling an organic phase at a definite temperature to form organogel [8]. Microscopy of the organogels showed that the 3D network of needle aggregates of gelator is responsible for immobilizing the apolar solvent. Non-ionic surfactants such as sorbitan esters or Spans are being currently employed for capping the non-polar phase in pharmaceutical, food, and cosmetic industries [9]. Due to their low cost and stability over a wide range of temperature, sorbitan esters are quite often being used as an alternative to the phospholipids for various topical preparations [10]. Sorbitan esters are generally classified according to the presence of fatty acid chain in their chemical structure. Presence of long saturated hydrocarbon chains within the sorbitan ester molecules results in the formation of solid esters (e.g., sorbitan monopalmitate [SP or Span 40] and sorbitan monostearate [SS or Span 60]) whereas, the short hydrocarbon chains form liquid esters (e.g., sorbitan monolaurate or Span 20). SP and SS have been found to be biocompatible, odorless, and form opaque, thermoreversible semi-solid oleogels with apolar liquids such as vegetable oil (soybean oil, sunflower oil, mustard oil, groundnut oil, olive oil, etc.) and dichloromethane [7]. SS and SP based organogels have potential applications as delivery vehicles for drugs and antigens [11].

Satapathy et al. reported that the mustard oil and groundnut oil based Span 40 organogel was opaque, thermoreversible, pseudoplastic and thixotropic in nature, and has huge potential to be used as the controlled delivery vehicle. Thermal stability of groundnut oil based organogels was found to be more than the mustard oil based organogels [12]. Rushikesh et al. described the development of Span 60 based organogel using sunflower oil as an apolar phase [13]. Shah et al. (2013) reported that organogel was formed due to entanglement of olive oil molecules within the tubular structure of gelator molecules of Span 40 and Span 60. Differential scanning calorimetry (DSC) and gel disintegration studies suggested that the Span 60 based organogels were having higher thermal...
and physical strength as compared to the Span 40 based organogels [14].
The use of sorbitan esters for the development of organogels has thus
opened up a new field of study.

Soybean oil-based organogel or soy-gel with Span 40 or Span 60 may be
formulated as a topical base for drug incorporation due to soybean oil's
stability to oxidation which is limited by its linolenic acid content [15].
In the present investigation, attempts were made to develop and
compare sorbitan monopalmitate and sorbitan monostearate based
soy-gels for topical applications.

Till date, no comparative analysis has been carried out on Span 40
and Span 60 based soy-gels which can enable choice of a suitable
soybean-oil based topical base for controlled drug delivery for release of
various active molecules. Since the two selected sorbitan esters
are structurally different, they are expected to produce organogels
having varying characteristics such as thermal properties, viscosity,
and drug release behavior and may exhibit differences in stability
profile.

**MATERIALS AND METHOD**

**Materials**

Food grade soybean oil (Emami Ltd., Kolkata, West Bengal, India)
was purchased from the local market. Paracetamol IP (PCM) was
received as a gift sample from the enlisted vendor. Span 40 (sorbitan
monopalmitate, SP) and Span 60 (sorbitan monostearate, SS) were
purchased from Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, India. All
other reagents were of analytical grade.

**Methods**

**Method of preparation of organogel**

Soybean oil was maintained at 60°C to which 2% w/v PCM was
added slowly with constant stirring on mechanical stirrer (REMI) at
500 rpm. Organogelator (Span 40 or Span 60) was added to the oil
and stirred for 1 h when a clear homogeneous solution was obtained.
Subsequently, the mixture was allowed to cool down to 25°C. If the
mixture failed to flow when inverted vertically, it may be considered
to form organogel. Span 40 (SP) and Span 60 (SS) based soy-gels
were formulated using varying concentrations of each organogelator
and composition is given in Table 1. The formulations were stored in
glass vials at 25°C for further characterization after 72 h. For each
organogel, there exists a critical gelator concentration (CGC) which is
induced [16].

**Characterization of soy-gels**

**Fourier transform infrared (FTIR) study**

Compatibility study of blank as well as drug loaded organogel along with
its individual components was carried out using FTIR Spectrometer
(ALPHA-II, Bruker, Billerica, MA, USA) operated in attenuated total
reflectance mode [17]. Samples were scanned in the range of 4000–
500/cm.

**Organoleptic evaluation**

Organogels were observed visually for their color, appearance, texture,
and opacity [18].

**Table 1: Composition of organogels**

| Ingredients (%) (w/v) | SP1 | SP2 | SP3 | SP4 | SS1 | SS2 | SS3 | SS4 |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Soybean oil          | 82  | 80  | 78  | 76  | 82  | 80  | 78  | 76  |
| PCM                  | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   |
| Span 40              | 16  | 18  | 20  | 22  | -   | -   | -   | -   |
| Span 60              | -   | -   | -   | -   | 16  | 18  | 20  | 22  |

Blank gels were named as SP* and SS* and used for characterization studies
other than in vitro drug release study. *Indicates drug-free organogels.
SP: Sorbitan monopalmitate, SS: Sorbitan monostearate

**pH determination**

The pH of the formulations was determined using a digital pH meter
(Fisher Scientific-Accumet AE 150) [18].

**Extrudability**

A fixed weight of organogel was filled into an ointment tube and
cremped. The extrudability (cm/s) of gel was determined by measuring
the length of the gel ribbons extruded from the ointment tube by applying
uniform pressure over a period of 10 s [19]. The following equation was
used to determine extrudability.

\[ \text{Extrudability} = \frac{\text{Distance travelled by the gel (cm)}}{10 \text{ s}} \]  

**Spreadability**

Spreadability of the formulations was determined by placing 0.1 g
formulation between two glass slides of equal dimensions (75 mm ×
25 mm × 1 mm). Thereafter, known weights of 10 g, 20 g, 50 g, or
100 g were loaded separately on the upper slide for 60 s. The initial
and final spreading diameters were marked before and after placing
the weight [20]. Finally, the percentage spreadability may be calculated
using the following equation (2).

\[ \% \text{Spreadability} = \left( \frac{D_i - D_f}{D_i} \right) \times 100 \]  

Where, \( D_i \) = initial spreading diameter, \( D_f \) = final spreading diameter

**Viscosity**

The viscosity of the blank gels (SP* and SS*) was measured in Brookfield
Digital Viscometer (Model DV+DV1, Brookfield Engineering Laboratories
Inc, USA) with spindle no. 6 at 1 rpm for 1 min at 25°C [21].

**Gelation kinetics study**

Gelation kinetics study of the blank soy-gels was carried out by
measuring the intensity of turbidity against time elapsed. Initially,
organogel was found to exist in a transparent sol state which became
 turbid with time due to the formation of a gel. Change from sol to
gel state was reflected as an increase in nephelometric turbidity
unit (NTU) as measured using a Nepheloturbidimeter (ELICO CL-
52D Nephelometer). Soybean oil was taken as sample blank and
the intensity of the turbidity of the organogel was measured at 10 s
intervals. The time at which turbidity attained a constant value
was defined as gelation time. The result is represented graphically
to observe the change in the gelation process with organogelator type
and concentration.

Gompertz model was employed for modeling of gelation kinetics [22].
This non-linear model indicates a relationship between turbidity
intensity (NTU), the concentration of gelator in % w/v (\( \rho \)) and time for
gelation in h (t).

\[ \log Y = \alpha + \beta \rho t \]  

\( Y \) is defined as oil parameter and is related to gel flexibility whereas
\( \beta \) indicates a characteristic property related to organogelator or can
be defined as organogelator parameter and is related to the thermal
stability of gel.

**Determination of gel-sol transition temperature**

The gel-sol transition temperature (T_g) of the organogels was
determined by the falling ball method [23]. Briefly, a metal ball of
weight 250 mg was placed gently on the surface of the soy-gel taken in
a beaker. A thermometer was inserted in the gel, and the gel was heated
from 25°C to 70°C at a rate of 1°C/min. The temperature at which the
ball started to move from the surface through the gel was recorded as
the gel-sol transition temperature (T_g).
Drug release study

In vitro drug release study

In vitro drug release from organogels was performed through a dialysis membrane (HIMEDIA LA 330-5MT) in modified Franz diffusion cell [26]. Accurately weighed drug-loaded sample containing drug equivalent to 4 mg was placed in the donor compartment and the receptor chamber containing phosphate buffer (pH 5.8) was maintained at 32°C ± 0.5°C. An aliquot of 1 ml of buffer was withdrawn every hour, replenished with fresh buffer and study was continued for 6 h. The aliquot was analyzed spectrophotometrically at 249 nm (Shimadzu UV-Vis 1800 spectrophotometer) [25]. The drug content of formulations was determined from the calibration curve of the drug in the said buffer.

Drug release data were subjected to mathematical modeling using zero-order, first-order, Higuchi, and Korsmeyer-Peppas model [27].

Hemocompatibility study

Accurately weighed the amount of blank organogel was placed in dialysis tube filled with 50 ml normal saline (0.9% w/v NaCl solution) and continuously stirred in a magnetic stirrer for 1 h at 37°C to enable leaching of the soy-gel components. Leachant (0.5 ml) was withdrawn, diluted to 10 ml with normal saline and 0.5 ml diluted goat blood (4 ml of goat blood diluted with 5 ml of normal saline) and incubated at 37°C for 1 h. It was then centrifuged at 3000 rpm for 10 min. The supernatant was measured spectrophotometrically at 542 nm. The positive control was prepared by taking 0.1 (N) HCl solution in lieu of leachant. Normal saline was used instead of leachant. Normal saline was taken as the corresponding blank and percent hemolysis may be calculated as follows:

\[
\text{% Hemolysis} = \frac{\text{OD}_{\text{test}} - \text{OD}_{\text{negative}}}{(\text{OD}_{\text{positive}} - \text{OD}_{\text{negative}})} \times 100 \quad (4)
\]

Table 2: Organoleptic characterization of Span based soy-gels

| Formulation | Color          | Odor          | Appearance       | Opacity       |
|-------------|----------------|---------------|------------------|---------------|
| SP1*        | -              | -             | -                | -             |
| SP2         | Yellowish white| Odorless      | Smooth-oily      | Slightly opaque|
| SP3         | Yellowish white| Odorless      | Smooth-oily      | Slightly opaque|
| SP4         | Yellowish white| Odorless      | Smooth-oily      | Slightly opaque|
| SS1         | Creamy white   | Odorless      | Smooth-oily      | Opaque        |
| SS2         | Creamy white   | Odorless      | Smooth-oily      | Opaque        |
| SS3         | Creamy white   | Odorless      | Smooth-oily      | Opaque        |
| SS4         | Creamy white   | Odorless      | Smooth-oily      | Opaque        |

*Indicates no gel formation. SP: Sorbitan monopalmitate, SS: Sorbitan monostearate

Table 3: Extrudability, spreadability, and hemocompatibility studies on Span based soy-gels

| Formulation | Extrudability* (cm/s) | Percentage spreadability on application of | Hemocompatibility |
|-------------|-----------------------|-------------------------------------------|-------------------|
|             |                       | 10 g | 20 g | 50 g | 100 g |                  |
| SP2         | 0.7±0.32              | 15.72| 27.12| 65.52| 85.62| Pass             |
| SP3         | 0.8±0.37              | 16.35| 23.15| 47.5 | 55.10| Pass             |
| SP4         | 0.6±0.41              | 13.56| 22.09| 45.98| 53.89| Pass             |
| SS1         | 0.76±0.31             | 36.92| 45.92| 77.16| 97.60| Pass             |
| SS2         | 0.75±0.24             | 42.73| 62.85| 75.89| 88.18| Pass             |
| SS3         | 0.78±0.35             | 37.49| 45.26| 74.85| 92.76| Pass             |
| SS4         | 0.76±0.16             | 33.33| 46.15| 57.89| 97.43| Pass             |

*Indicates no gel formation. SP: Sorbitan monopalmitate, SS: Sorbitan monostearate

RESULTS

Organogel formation

The CGC for Span 60 was found to be 16% w/v (SS1) and 18%w/v for Span 40 with soybean oil (SP2).

Organoleptic evaluation

Span 40 and Span 60 based soy-gels were found to be closely identical in their organoleptic properties except color and degree of opacity (Table 2). Increase in consistency on increasing concentration of the organogelator was visible in both Span 40 and Span 60 based soy-gels. pH of the formulations was found to be between 5.5 and 5.8 at 25°C which is compatible with skin.

FTIR study

The FTIR study of blank as well as drug-loaded organogels revealed the characteristic peaks of individual gel components and drug. The FTIR spectral analysis of Span 40 and Span 60 showed an O-H stretching peak at 3300/cm whereas Span 40 and Span 60 based organogels did not show any O-H stretching vibration at 3300/cm (Fig. 1).

Extrudability and spreadability study

Extrudability of the Span 40 and Span 60 based organogels was found to be satisfactory. The percent spreadability of Span 40 and Span 60 based organogels is shown in Table 3.

Viscosity

Different organogel formulations showed concentration-dependent increase in viscosity(Table 4). Viscosity of Span 60 based soy-gels was found to be 10 times higher than that of Span 40 based formulations.

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Asian J Pharm Clin Res, Vol 12, Issue 6, 2019, 259-265

Mukherjee et al.

Drug content determination

A definite amount of drug-loaded soy-gel was mixed with phosphate buffer (pH 5.8) to produce a uniform dispersion which was kept undisturbed for 48 h [24]. The dispersion was filtered through Whatman filter paper No. 1. An aliquot of the filtrate was suitably diluted and absorbance measured spectrophotometrically at 249 nm (Shimadzu UV-VIS 1800 spectrophotometer) [25]. The drug content of formulations was determined from the calibration curve of the drug in the said buffer.

% Hemolysis = \((\text{OD}_{\text{test}} - \text{OD}_{\text{negative}})/(\text{OD}_{\text{positive}} - \text{OD}_{\text{negative}})\) × 100 \hspace{1em} (4)

Accelerated thermal stability study

The stability analysis of the pharmaceutical products may be carried out either by a thermo cycling process or by incubating the samples at a specific environment for a longer period of time [29].

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 [30]. Results are quoted as significant where p<0.05.
Gelation kinetics study
The parameters related to soy-gel flexibility and thermal stability, $\alpha$ and $\beta$ are reported in Table 5.

Determination of gel-sol transition temperature
Gel-sol transition temperature ($T_g$) of Span 40 based soy-gels was found to be in the range of 42°C–48°C whereas it was in the range of 56°C–63°C in case of Span 60 based formulations (Table 4).
Drug content study
Drug content of SP-based soy-gels was found to be in the range 95–98% and it was lower (90–93%) in SS based soy-gels.

In vitro drug release study
In vitro, drug release study revealed 50.81% drug release from SP2 in 6 h and 47.34% drug released from Span 60 based soy-gel at its CGC (SS1; 16% w/v) (Fig. 2). Increase in organogelator concentration reduced drug release. Soy-gel with a higher concentration of Span 40 (SP3 and SP4) followed Korsmeyer–Peppas kinetics with non-Fickian diffusion. At CGC, Span 40-based soy-gel (SP2) released the drug by Fickian diffusion. Span 60 based soy-gels manifested remarkable change in release kinetics as three formulations (16–20% w/v Span 60) (SS1, SS2, and SS3) followed zero-order kinetics with non-Fickian diffusion except SS4 which followed Korsmeyer–Peppas model (Table 6).

Hemocompatibility study
The percentage hemolysis of all the formulations was found to be <5% in presence of organogel leachant (Table 3).

Accelerated thermal stability study
Change in gelation time after each thermocycler of freeze-thaw for Span 40 and Span 60 based soy-gel has been graphically represented to determine gel stability after subjecting to specified temperature fluctuations (Fig. 3).

DISCUSSION
Formation of soy-gel occurred owing to lowering of the solubility parameter of Span 40 and Span 60 and precipitation of the gelator molecules as the temperature was reduced. This may be due to the interaction between the hydrophobic components of the gelator fibers thereby forming a 3D network structure of gelator, and immobilized soybean oil with drug molecules entrapped within solid fiber organogels [31]. The difference in CGC was noted for soybean oil with a change in Span indicating difference in the ability to induce gelation with change in structure of organogelator [32]. FTIR study indicated compatibility among organogel components and also the existence of PCM in native state within drug-loaded gel. Absence of O-H peak in organogel indicates recession of the O-H stretching within the gelator molecules [33].

Extrudability is one of the important mechanical characteristics of a gel which confirms the structural behavior on application of fixed pressure into a specific area. Spreadability is behavior of a gel that ensures mechanical strength and total integrity upon application. Soy-gels formulated with Span 40 and Span 60 are expected to spread uniformly over the affected area of skin on being extruded without loss of structural integrity. The formulations may be regarded as hemocompatible as percentage hemolysis was <5% [34].

Viscosity is an important property of gel-like formulations [35]. Addition of Span 60 increased the viscosity of soy-gels probably due to its better ability to form gels in comparison to Span 40.

As the temperature of the organogels was increased, there was a corresponding increase in surface free energy with subsequent increase in mobility of the gelator molecules constituting the 3D-self assembled structure of the formulations. With further increase in temperature the interaction between self-assembled structure was totally disrupted leading to the breakdown of networked structure, thereby causing the gelled system to acquire sol state and flow freely [36]. It is to be noted that gel-sol transition temperature of Span 40-based organogels was considerably lower relative to corresponding Span 60-based formulations. Moreover, gelation times were lower with Span 60 based soy-gels. In both the cases, gel-sol transition temperature increased and gelation time decreased with increase in concentration of organogelator (Table 4). The differences in organogel behavior may be attributed to better networking ability of Span 60 compared to Span 40. Critical comparison of Span 40-and Span 60-based soy-gels was done on the basis of gelation kinetics study through the determination of α and β parameters related to gel flexibility and thermal stability of the soy-gels, respectively. As the concentration of gelator was increased in both Span 40 and Span 60 based soy-gels, a value (flexibility) decreased indicating formation of comparatively rigid gels with higher viscosity (SP4 and SS4) and

Table 6: Modeling of drug release kinetics from Span based soy-gels

| Formulation | Zero-order model | Korsmeyer-Peppas model | Best fit model |
|-------------|------------------|------------------------|---------------|
|             | R²               | R²                     | n             |                 |
| SP2         | 0.9909           | 0.9438                 | 0.45          | Zero-order with Fickian diffusion |
| SP3         | 0.995            | 0.9988                 | 0.76          | Korsmeyer–peppas with non-Fickian diffusion |
| SP4         | 0.985            | 0.9934                 | 0.60          | Korsmeyer–peppas with non-Fickian diffusion |
| SS1         | 0.999            | 0.745                  | 0.77          | Zero-order with non-Fickian diffusion |
| SS2         | 0.999            | 0.755                  | 0.57          | Zero-order with non-Fickian diffusion |
| SS3         | 0.996            | 0.960                  | 0.56          | Zero-order with non-Fickian diffusion |
| SS4         | 0.979            | 0.9941                 | 0.7261        | Korsmeyer–peppas with non-Fickian diffusion |

SP: Sorbitan monopalmitate, SS: Sorbitan monostearate
better thermal stability as manifested in increasing β-value and higher Tc (Table 4). Soy-gels containing Span 40 as organogelator were found to possess higher flexibility (α) compared to corresponding Span 60 based soy-gels. Although Span 40 gels are having a higher β value indicating higher thermal stability, the Tc values of Span 60 gels were found to be higher with corresponding lower β-values. This can be explained by the ability of Span 60 to impart higher thermal stability to gels at comparatively lower β value which indicates firmness of the structure attributed by Span 60 [14:31]. A similar report of better thermal strength of Span 60 based olive oil organogels is already existing in literature [14]. Since, Span 60 was found to show lower CGC (16% w/v) compared to Span 40 (18% w/v) for soy-gel and imparts better thermal stability, Span 60 may be assumed to have modified microarchitecture of soy-gels. The Span 40 based formulations with higher α value (SP2 and SP3) and lower viscosity are expected to exhibit improved drug release.

Drug release data from Span 40 and Span 60 based soy-gels revealed major differences. All the formulations released approximately 40–50% drug (PCM) in 6 h except SS2, SS3, and SS4. SS1 (16 w/v% Span 60) demonstrated better release than SP3 and SP4. It is to be noted that enhanced drug release was found from Span 40 based soy-gels as expected from gelation kinetics study and viscosity data. Improved drug release is thus attributed to the flexible structure of Span 40 gels and probably amorphous nature of the gels [37]. Poor drug release from soy-gels necessitates the development of strategies to improve organogel formulation.

Kinetic modeling of drug release data revealed non-Fickian drug diffusion from gels with increasing concentration of Span 40 (with 20% w/v and 22% w/v Span 40) which exhibited Korsmeyer-Peppas model. However, zero-order drug release or nearly constant concentration-independent release was observed in SP2 and all Span 60 formulations except SS4. Fickian diffusion was detected only in soy-gels with the least concentration of Span 40. Ideally, the lowest concentration of Span 40 gels (18% w/v) and Span 60 gels (16-20% w/v) can be selected as topical bases for controlled drug release [38].

The formulations were found to be stable after five thermocycles with no visible signs of instability. However, the gelation time of both SP and SS based soy-gels was increased gradually. It may be said that there was a change in the network structure of the gels due to consecutive heating and cooling. CONCLUSION

From the above studies, it can thus be concluded that type and concentration of organogelator has a profound influence on the viscosity, flexibility, thermal stability, and drug release behavior of soybean oil-based soy-gel intended for topical application to achieve controlled release.

AUTHORS’ CONTRIBUTIONS

The present research work is a part of M Pharm thesis work of first two authors under the guidance of last 2 authors and all have equally contributed in writing and editing the manuscript at various stages.

CONFLICTS OF INTEREST

All authors have none to declare.

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