Dipanjana Ash et al /J. Pharm. Sci. & Res. Vol. 11(5), 2019, 1796-1802

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Soybean Oil-Hpmck15M Based Oleohydrogel Hybrid: Novel Approach to Improve Drug Release

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Abstract

Aims: The objective of the present investigation was to develop and characterise soybean oil-HPMCK15M based oleohydrogel hybrid to achieve controlled and improved drug release. **Method:** Paracetamol loaded oleohydrogel hybrid was prepared by dispersing soybean oil-Span 40 based oleogel into hydrogel developed with varying concentrations of HPMCK15M and were subjected to organoleptic, applicability characterisation, FT-IR study, evaluation of thermal behaviour, rheological property and kinetic modelling of drug diffusion and determination of diffusion parameters.

Results: Oleogel and oleohydrogel hybrids revealed chemical compatibility from FT-IR study and satisfactory organoleptic and applicability parameters. Gelation time of oleohydrogel hybrids decreased with increase in HPMCK15M concentration and they exhibited pseudo-plastic flow. Drug diffusion from oleohydrogel hybrid containing 18%w/v Span 40 and 1.5% w/v HPMC (OH1) demonstrated better drug release (60-70%) whereas the corresponding oleogel (OG) released 55% paracetamol at the end of 7 hr in phosphate buffer (pH 5.8), exhibited zero order kinetics with non-Fickian and Fickian diffusion respectively. However, hybrid formulations with higher HPMC formed gel- matrix followed Higuchi model with non-Fickian and super case II transport.

Conclusion: The novel strategy of formulating soybean oil-HPMCK15M based oleohydrogel hybrid formulations may thus be adopted to improve rheological behaviour as well as drug release from topical formulations.

Keywords: Fickian diffusion, HPMCK15M, Oleogel, Oleohydrogel hybrid, Soybean oil, Span 40

INTRODUCTION

Oleogels are semi-solid, thermo-reversible viscoelastic systems, where an apolar phase gets immobilized within the spaces of the 3-D network formed by physical interactions amongst the self-assembled structures of organogelators (various grades of Spans, polycarbonate, polyesters, N-lauroyl-L-lysine ethyl ester etc.) [1-4]. These drug delivery vehicles resist microbial contamination and possess several advantages over conventional gels [5]. An ideal topical oleogel for controlled drug delivery should exhibit non-Newtonian flow, be thermally stable and follow zero-order kinetics during drug diffusion [1]. Studies reported poor drug release (<50%) from vegetable oil based organogel with 20-22%w/v Span 40 or Span 60 [2-3]. Hence, to improve drug release pattern, a novel strategy, oleohydrogel hybrid or bigel can be developed for topical use with oleogel as the lipophilic phase and hydroxy propyl methyl cellulose (HPMC) hydrogel as aqueous phase. Several studies have reported bigel formation with natural and synthetic hydrophilic polymers such as guar gum, Carbopol, HPMC, PVPK30 [6-9]. As HPMC undergoes swelling during penetration of dissolution medium it expands the oleogel mesh probably increasing the mesh porosity and accelerating influx of aqueous solvent to the core of the hybrid. This may facilitate enhanced drug release from the hybrid [10].

To achieve controlled and improved drug release from topical preparation, none has previously attempted to form oleohydrogel hybrid of soybean oil-based oleogel with Span 40 and employing HPMCK15M as the gelling agent in the aqueous phase. The objective of the present investigation was to develop, characterise soybean oil-HPMCK15M based oleohydrogel hybrid and compare it with oleogel on the basis of rheological property and drug diffusion parameters.

MATERIALS AND METHODS

MATERIALS

Soybean oil (Emami Ltd., Kolkata) was procured from local market, Kolkata, West Bengal. Span 40 and Tween 80 were of AR grade and obtained from Loba Chemie (India) and Merck Specialities Pvt. Ltd (India) respectively and paracetamol IP (PCM) was received as a gift sample from enlisted vendor. HPMCK15M was of AR grade and obtained from Colorcon Asia Pvt. Ltd. as gift sample. Double-distilled water was used throughout the study, wherever required. For hemocompatibility study, fresh goat blood was collected in heparin coated tube and stored at -4ºC.

METHODS

Preparation of oleohydrogel hybrid

Accurately weighed Span 40 and paracetamol (2% w/v for drug-loaded batches) were 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 and it was allowed to cool down subsequently to 25ºC to form an 18% w/v oleogel on gelation. Hydrogels of 3 different concentrations were prepared by dispersing accurately weighed HPMCK15M in hot water (60 ºC) and stirring continuously. The heated oleogel in sol state was added drop wise into the hydrogel at 60ºC and stirred continuously at 500 r.p.m to form a creamy, homogeneous oleohydrogel hybrid. The formulations were stored in glass vials at 25ºC and considered to be gel if they did not flow on inversion. Oleohydrogel hybrids were prepared by varying concentrations of HPMC-based hydrogel and mixing with a fixed percentage of oleogel according to the composition given in table 1.

Characterisation of formulations

Fourier Transform Infrared (FT-IR) Spectroscopy:

Infrared spectroscopy of oleohydrogel components and the formulations (OG, OG′, HG 2′ and OH 2) were carried out by FT-IR spectroscopy (Bruker, Alpha-T, Germany) in attenuated total reflectance (ATR) mode in the range of 4000-500cm^{-1}.

Organoleptic evaluation:

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

Evaluation of applicability parameters [11]**:**

Applicability parameters for topical preparation include determination of extrudibility and spreadability. Extrudibility of oleogels and oleohydrogel hybrid was studied by filling the formulation into a collapsible tube followed by measuring the distance travelled by the ribbon of extruded gel in 10 s. Spreadability study was carried out by placing approximately 1 g of gel (oleogel and oleohydrogel hybrid) between two glass slides of equal area and thickness (75mm*25mm*1mm). Initial spreading diameter (D_i) was noted. Thereafter, a load of 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. Extrudibility and spreadibility are expressed as cm/s and in percentage respectively. The % spreadability of both gels was calculated as per the equation given below.

$$\% \text{ spreadability} = [(D_f - D_i)/D_i]^* 100 \quad \text{.....(1)}$$

pH measurement:

The pH was measured by immersing the glass electrode of the digital pH meter (EUTECH INSTRUMENTS pH Tutor) in the prepared gels at 25ºC.

Drug content estimation [12, 13]:

A definite amount of drug-loaded gel formulations was mixed with phosphate buffer (pH 5.8) to obtain uniform dispersion that was kept undisturbed for 48hr. The dispersion was filtered through Whatman filter paper (No.1). The aliquot of filtrate was suitably diluted and analysed by UV–visible spectrophotometer (UV 1800 UV-vis spectrophotometer, Shimadzu Corporation) at a wavelength of 249 nm.

Determination of gel-sol transition temperature (T_g) [3]:

Drop ball method was employed for determination of the gel-sol transition temperature (T_g) of oleogel. A stainless steel ball having the diameter of $1/8^{th}$ inch and weight of 230 mg was placed over the formulation in a beaker and attached with a melting point apparatus (EI-931, Electronics India). The formulation was heated at a rate of 1ºC/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). For oleohydrogel hybrid, similar data could not be collected due to turbid nature of the formulation on melting.

Gelation study:

Gelation study was performed by nepheloturbidometry (ELICO® CL 52D, ELICO India). Oleogel in sol state was transferred to Nessler cylinder and the light was allowed to pass through the turbid sample where suspended particles scattered light. Transformation of sol to gel was characterised by increase in turbidity which continued for a certain period of time after which there was no further increase in turbidity. The time at which turbidity attained a constant value is defined as gelation time. The turbidity intensity was measured at 20 s interval and expressed in terms of nepheloturbidity unit (NTU).

Determination of melt flow index [14]**:**

Melt flow index (MFI) is defined as the ease of melt flow of thermoplastic material in gram over a period of 10 min at a certain standard temperature (i.e, 65°C for gel formulations) when checked in melt flow tester. A fixed weight of oleogel (10 g) was poured into the cylinder and temperature was set at 65°C to prevent thermal degradation of gel at higher temperature as specified in reported method. Pressure was applied with the piston bar to the cylinder using 10 g of weight above the piston bar after setting the predefined temperature. Sample flow occurred through the die face in the form of wire and was collected after 10 min and was further subjected to weighing to determine its mass. Determination of MFI for bigel was not possible due to non-uniform flow of molten fraction of oleogel through the hybrid.

Rheological study [2]**:**

Rheological behaviour of oleogels and hybrid formulations was established from their viscosity profile. Viscosity was determined by Brookfield digital viscometer (Model LVDVI+) at 25ºC by varying shear rate from 1-5 r.p.m (spindle 6) for 1 min each. Ostwald de-wale Power model (equation 2) was employed for modelling of viscosity for the determination of flow consistency index (k) and flow behaviour index (n) from the relationship between shear stress (Ƭ) and shear rate (ɤ).

$$Ƭ = k^* ɤ^n \quad \text{..... (2)}$$

In vitro drug diffusion study [13]:

Modified Franz diffusion cell was used to perform the in vitro drug release study from prepared gel formulations through dialysis membrane-60 (HIMEDIA® LA 330-5MT). Accurately weighed drug-loaded gel containing PCM equivalent to 4 mg 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±0.5ºC. An aliquot of 1 ml was withdrawn every hour for 7h and replenished with fresh buffer. Following appropriate dilution, aliquot was analysed by UV–visible spectrophotometer (UV 1800 UV-vis spectrophotometer, Shimadzu Corporation) at a wavelength of 249 nm. From drug release profile the time taken for diffusion of 50 % drug i.e, t_{50} value was calculated for all gel formulations for model-independent comparison. Simultaneously, the drug release data of gels were subjected to kinetic modelling to determine the drug release pattern and the diffusion mechanism.

Determination of steady-state flux and permeability co-efficient [15]:

The measurement of flux across human skin provides a valuable insight into the formulation development of any dermatological product. The steady-state flux of PCM from both oleogels and oleohydrogel hybrid across the artificial dialysis membrane is defined as follows.

$$SS_{flux} = dQ/dt^*1/A \quad \text{.....(3)}$$

Where,

SS_{flux}= steady-state flux of drug (mg/cm^2.hr); dQ/dt= slope of the linear portion of the curve i.e. cumulative amount per unit time (mg/hr); A = diffusional area (cm^2)

Permeability co-efficient is quantified by the following equation.

$$K_p = SS_{flux} / C_{app} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where,

C_{app} = initial concentration of the drug in the gel formulation. In the present study, it was expressed as %w/v i.e. weight of drug actually present in the volume of gels taken for the permeation study.

Hemocompatibility study [16] **:**

Accurately weighed (1g) oleogel as well as bigel was placed inside dialysis tubing, immersed in 50 mL of normal saline and incubated at 37°C for 1 h in a shaker incubator so as to allow the leaching of the components from the gels. 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 analysed at 545 nm using UV-visible spectrophotometry. The test measures the extent of haemolysis in the presence of the bigel. Percent haemolysis is calculated by the formula.

$$\% \text{ Hemocompatibility} = (OD_{test}-OD_{negative})/(OD_{positive}-OD_{negative}) \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Where,

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

Accelerated stability study [3], [16] **:**

Accelerated stability study includes thermo-cycling or freeze/thaw cycling, and syneresis measurements that help to predict the effect of temperature change on stability of not only the anhydrous organogels but also biphasic gel formulation. The purpose of the study was to assess the change in gelation time with consecutive freeze-thaw cycles.

Thermo-cycling or freeze-thaw cycling method involves incubation of the freshly prepared gel samples at 65ºC for 15mins till the formation of sol state followed by gelation when time was noted. Then these gel formulations were incubated at 4ºC for 15 min after which stored at 25ºC for 48hr. The cycle was repeated for 5 cycles for oleogel and its hybrids.

RESULTS

Oleohydrogel hybrid formation:

No phase separation or colour change was observed visually in the formed oleohydrogel hybrid.

Fourier Transform Infrared (FT-IR) spectroscopy:

The FT-IR profile is presented in figure 1. Peaks at 2913, 2855, 1744, 1157 and 719 cm^{-1} were observed in the spectrum of soybean oil. Most of the characteristic peaks of Span 40, soybean oil, drug and HPMCK15M were visible in blank (OG′), drug-loaded oleogel (OG), oleohydrogel hybrid (OH 2′) and hydrogel (HG 2).

Organoleptic evaluation:

The organoleptic properties of prepared formulations are summarized in table 2. OG was found to be yellowish-white in colour, odourless and opaque in nature, smooth-oily in touch, but after mixing with hydrogel, the oleohydrogels (OH 1, OH 2 and OH 3) became creamy in nature and acquired milky-white colour and smooth texture.

Evaluation of applicability parameters

All these gel formulations demonstrated satisfactory applicability parameters as evident from table 2.

pH measurement:

The pHs of all of the formulations were found to be between 5.5-5.8±0.3 at 25ºC.

Drug content estimation:

The drug content of oleogels was found to be in the range of 97-98% and % was found to be unchanged in the hybrids.

Determination of gel-sol transition temperature and gelation time:

Gel-sol transition temperature and gelation time of OG were found to be 42±0.1ºC and 1060 sec respectively. The gelation time for oleohydrogel hybrids varied between 389-456 sec and can be ranked for formulations as: OH 1> OH 2> OH 3.

Rheological study:

Viscosity decreased with increase in shear rate (r.p.m) for all the prepared formulations. The magnitude of viscosity of formulations followed the order OG< OH 1< OH 2< OH 3. The flow behaviour index (n) was found to be less than 1 from Ostwald de-wale Power model. The viscosity profile is graphically represented in figure 2.

Melt flow index:

MFI of OG was found to be 0.87gm/ 10mins but for OHs MFI could not be determined as mentioned previously.

In vitro drug diffusion study:

The drug release profile of PCM from the prepared gels has been shown in figure 3. Kinetic modelling of drug diffusion is represented in table 3. The order of t_{50} values of gel formulations are as follows: OH 3> OG> OH 2> OH 1.

Determination of steady-state flux and permeability co-efficient:

Steady-state flux and permeability co-efficient of the formulations are represented in table 4. OH 1 exhibited higher SS_{flux} and K_p values compared to OG and other hybrid formulations, OH 2 and OH 3.

Hemocompatibility study [14]**:**

All the prepared formulations were found to be heamocompatible as the observed haemolysis was <5%.

Accelerated stability study:

After each cycle, percentage change in gelation time for all formulations is depicted graphically in figure 4. The order of percentage change in gelation time of oleohydrogel hybrid is given as: OH 1> OH 2> OH 3.

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 $p < 0.05$.

Table 1: Composition of oleogel, hydrogels and oleohydrogel hybrids					
	Concentration (%w/v)				
Batch	Span 40	Soybean oil	Paracetamol	HPMCK15M	Water
OG	18	80	2	-	-
HG1	-	-	-	1.5	98.5
HG 2	-	-	-	3	97
HG 3	-	-	-	4.5	95.5
OH 1	18	80	2	1.5	98.5
OH 2	18	80	2	3	97
OH 3	18	80	2	4.5	95.5
*OG′, HG 2′, OH 1′, OH 2′ and OH 3′are corresponding blank gels of OG, HG 2, OH 1, OH 2 and OH 3 respectively. Blank gels have been used for all studies except studies for determination of drug diffusion parameters.					

Table 2: Organoleptic and applicability evaluation of gel formulations					
Batch	**Organoleptic property**			**Applicability parameters**	
	Colour	**Odour**	**Appearance**	**Extrudibility (cm/s) (n=3)**	**Range in % spreadability with application of individual load**
OG	Yellow	Odourless	Smooth-oily	0.8±0.6	12-56
OH 1	Creamy-white	Odourless	Non- greasy	1.5±0.7	30-78
OH 2	Creamy-white	Odourless	Non- greasy	1.2±0.5	25-67
OH 3	Creamy-white	Odourless	Non- greasy	1.0±0.4	22-65

Table 3 : Modelling of drug release kinetics from gels				
Batch	**Best fit kinetic model**	**R^2**	**n**	**Diffusion mechanism**
OG	Zero order	0.9943	0.5	Fickian
OH 1	Zero order	0.9954	0.7053	Non- Fickian
OH 2	Higuchi	0.9957	0.7306	Non- Fickian
OH 3	Higuchi	0.9899	0.9802	Super case II

Table 4: Determination of t_{50}, steady state flux and permeability co-efficient of gel formulations (n=3)			
Batch	**t_{50} (hr)**	**SS_{flux} (mg/cm^2.hr)**	**K_p (cm^2/hr)**
OG	6.0±0.7	2.69±0.8	1.34±0.7
OH 1	4.5±0.4	3.49±0.5	1.75±0.4
OH 2	5.2±0.5	2.89±0.6	1.45±0.6
OH 3	6.2±0.3	2.48±0.4	1.24±0.5

DISCUSSION

Oleogel formation was promoted by temperature-induced change in solubility parameter of Span 40 molecules leading to decreased affinities between soybean oil and Span 40 molecules hence causing self-assembly of Span molecules into aggregates [3]. HPMCK15 forms a polymer gel network with water with increase in temperature [17]. Probably, presence of Span 40 promoted formation of uniform oleohydrogel hybrid where no phase separation could be detected between organic and aqueous phases. All these gel formulations demonstrated compatibility with skin pH indicating their suitability for topical application.

FTIR study revealed compatibility between the gel components indicating only physical interaction is responsible for formation of either oleogel or oleohydrogel hybrid.

Gelation study indicates faster formation (2-2.5 times) of oleohydrogel hybrids than the corresponding oleogel. Increase in HPMCK15M concentration from 1.5 to 4.5% w/v in hybrid formulations produced significant lowering (~17%) in gelation time.

Oleogel was found to be thermo-stable till 5 thermo cycles. However, in hybrid formulations, phase separation was detected after 5 cycles which is obvious due to immiscibility of apolar oil/oleogel phase and aqueous gel/sol phase. In 4th cycle, significant change in % gelation time (45% increases) was observed for OH1 in contrast to 1st cycle. Comparison of gelation time values for other hybrids indicates that the % change in gelation time in OH 3 with higher concentration of HPMC was approximately 1.5 and 1.1 times lower than OH 1 and OH 2 respectively due to presence of increased concentration of HPMCK15M. On the other hand, the % change of gelation time in OG was found to be negligible in the range of within 10% from 1st to 5th cycle. Thus, in order to ensure better shelf-life stability of oleohydrogel hybrid, temperature fluctuations should be avoided and preferably be stored at room temperature.

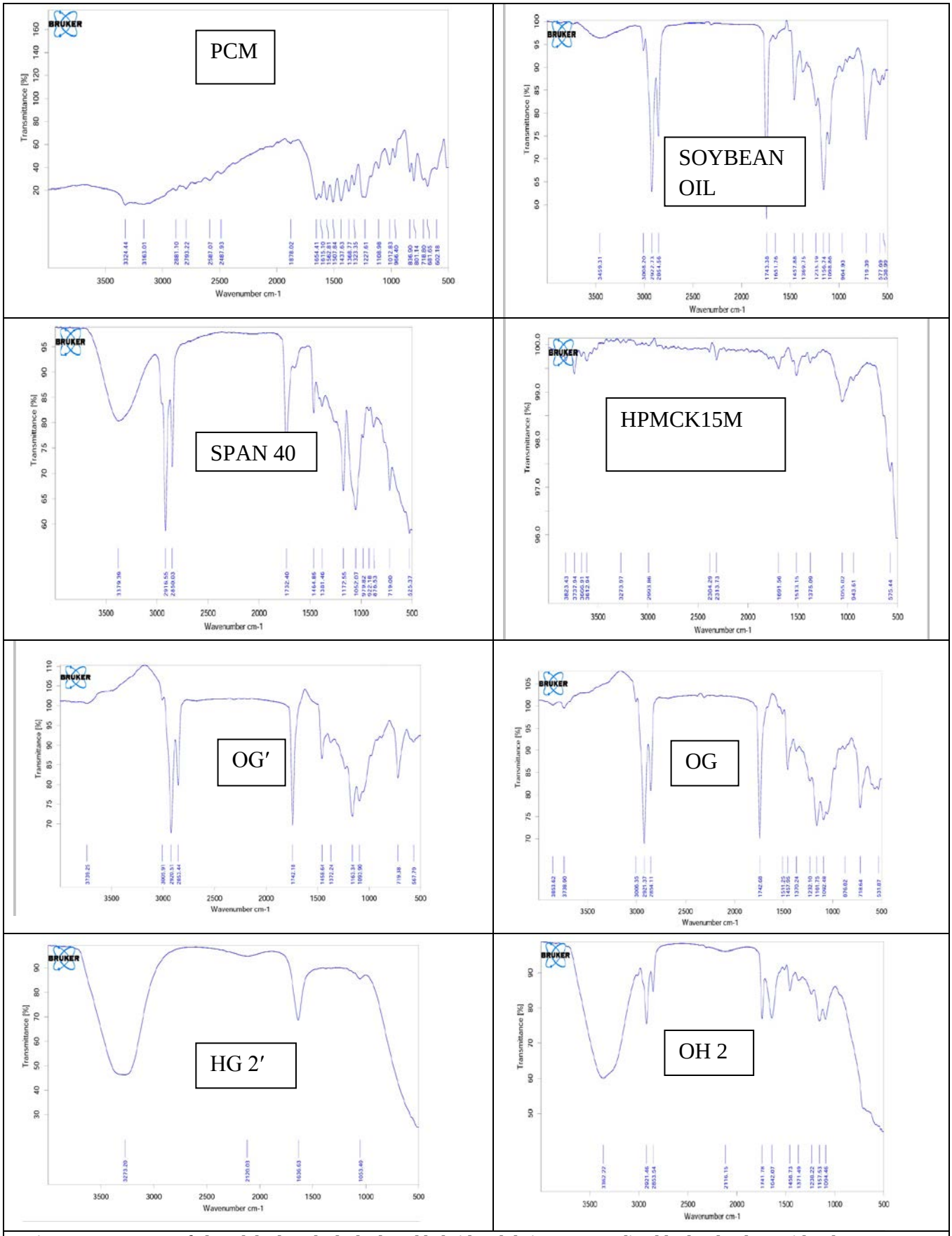

Fig 1: FT-IR spectra of oleogel, hydrogel, oleohydrogel hybrid and their corresponding blank gels along with gel components

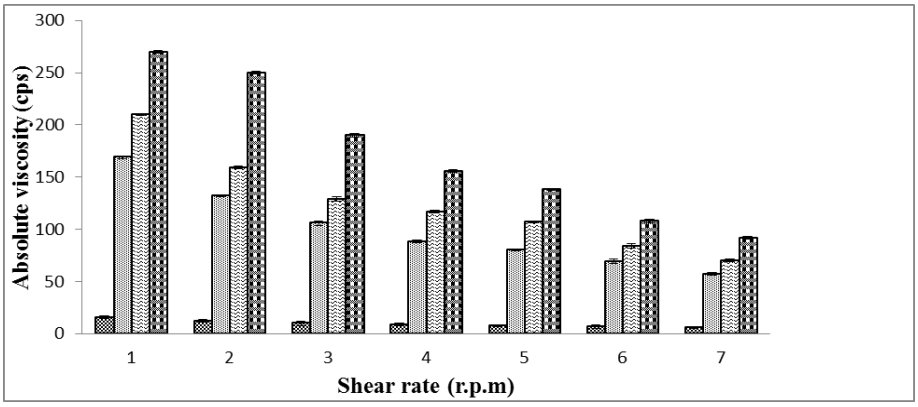

Fig 2: Viscosity profile of blank oleogel and oleohydrogel hybrids [OG′, OH′ 1, OH′ 2, OH′ 3. Error bars represent standard deviations for 3 experiments.

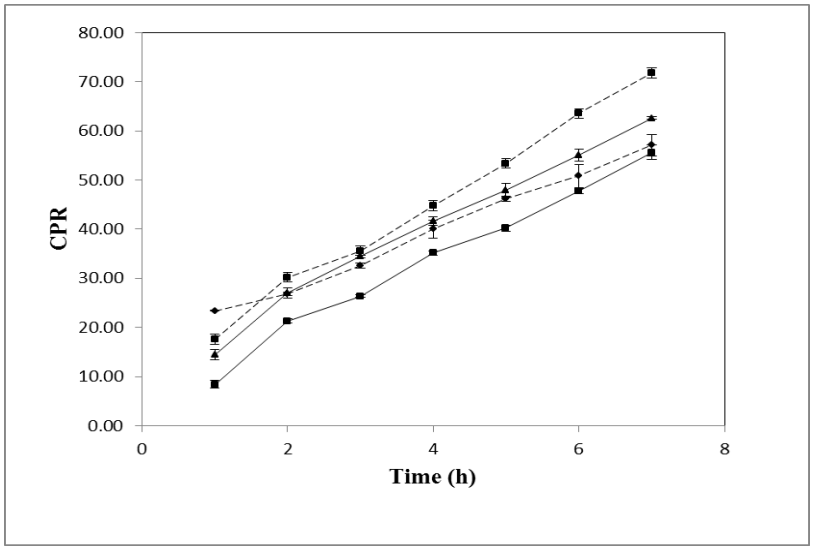

Fig 3: Drug release profile of gel formulations in phosphate buffer (pH 5.8) at 32±0.5ºC[- - ▪ - -OH 1, −▪− OH 3, --♦--OG, −▲−OH 2**] Error bars represent standard deviations for 3 experiments**

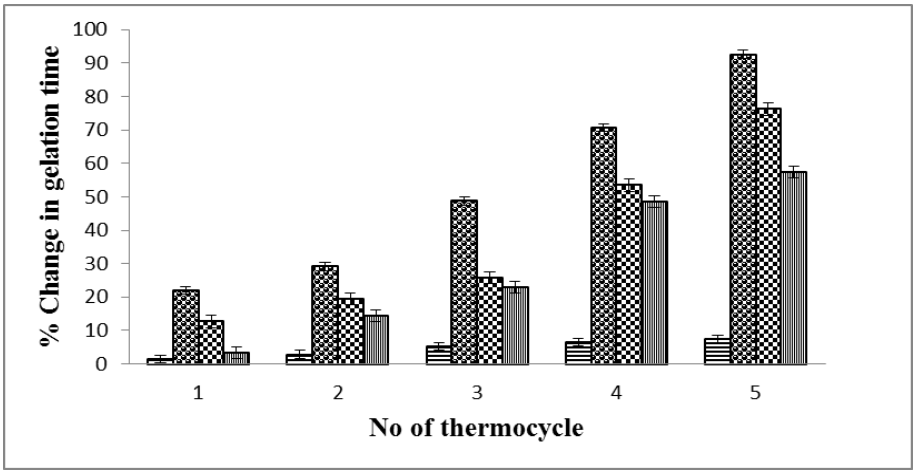

Fig 4: % change in gelation time for blank gel formulations with freeze-thaw cycles in accelerated stability study [OG ′, OH ′1, OH ′2, OH ′3. Error bars represent standard deviations for 3 experiments.

Rheological study revealed shear-thinning behaviour of oleogel and oleohydrogel hybrids, also confirmed by 'n' value <1 as calculated from Ostwald de- wale Power model equation [2]. Pseudo plastic flow is desirable for efficient topical delivery of drugs enabling the formation of a thin layer of the formulation over the skin surface [9]. The viscosity values of oleohydrogel hybrid, OH 1 were found to be 10 times greater than those of oleogel at all shear rates, indicating better mechanical strength of the hybrid. For each hybrid formulation, there was 1.5 times change in viscosity values as shear rate increased from 1 to 5 rpm.

It is already reported that increase in organogelator concentration reduces the percentage drug release from oleogel [2-3]. As 18% w/v Span 40 is the threshold concentration to induce gelation of soybean oil (OG) i.e., critical gelator concentration of Span 40 for soybean oil and the oleogel demonstrated maximum drug release of 57.08 % in 7h compared to other higher concentrations of Span 40 (data not shown), it has been chosen for oleohydrogel hybrid preparation with varying concentration of HPMCK15M. Oleohydrogel formation enhanced drug release at lower percentages of HPMC K15M compared to the native oleogel. Concentration-independent, zero-order drug release was observed in oleogel and OH1 via Fickian and non-Fickian diffusion phenomena respectively. But higher concentrations of HPMC K15M in OH 2 and OH 3 might have formed gel-matrix as drug release followed Higuchi model with non-Fickian and super case II transport mechanism respectively. This can be explained by the gradual break-up of the gel matrix into smaller fragments as the gel skeleton is compromised by the influx of dissolution medium via the conduits offered by the tubular structure of gelator molecules. Finally the drug-loaded oil droplets could be released [18]. But in case of oleohydrogel hybrid (OH 1 and OH 2), emulsification facilitated by the gelator molecules which are primarily surfactant, might have occurred earlier at the hybrid interface between the oleogel and hydrogel promoting faster and better drug release than oleogel(OG) [18]. Most probably, swollen but highly dense and compacted structure of HPMC hydrogel in OH3 could not induce maximum stressing and expansion of oleogel core and thus hindered drug release. Moreover, higher concentration of HPMK15M in OH 3 retarded the drug release from the gel-matrix due to formation of high-viscosity drug diffusion barrier. Results from studies on steady-state flux and permeability co-efficient of gel formulations indicate similar pattern as observed with drug diffusion study.

CONCLUSION

From the various studies conducted on soybean oil based oleogel and its hybrid with HPMCK15 hydrogel, it can be concluded that incorporation of hydrogel component to form oleohydrogel hybrid has produced significant improvement in rheological behaviour as well as drug diffusion parameters. Therefore, the novel strategy of formulating soybean oil-HPMCK15M based oleohydrogel hybrid may be adopted to improve drug release from topical formulations.

ACKNOWLEDGEMENT

The author(s) would like to acknowledge Department of Pharmacy, NSHM Knowledge Campus for providing an institutional research platform and necessary facilities.

CONFLICTS OF INTERESTS

All authors have none to declare.

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