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Research Article

A Novel Preparation Method for Organogels: High-Speed Homogenization and Micro-irradiation

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Abstract. The aim of this work was to prepare organogels of Carbopol 974P NF (C974) in PEG 400 by using a novel technique, high-speed homogenization followed by microwave heating. Triclosan (TCS) was used as a model drug. C974, at concentrations ranging between 2% and 4%, was dispersed in 25 ml of PEG 400, and the dispersion was homogenised for 5 min at 24,000 rpm. The dispersion was either heated at 80°C in water bath under mechanic stirring at 200 rpm or exposed to micro-irradiation (1,200 W/1 h) for 2 min. The formulations prepared with both methods performed a well-structured gel matrix characteristic at 3% and 4% of C974 concentrations. As the concentrations of the polymer increased, the elastic properties also increased. The viscosity profiles indicated a shear-thinning system. DSC data revealed that TCS was dissolved in gel. Skin accumulation ability of TCS had been improved by these novel organogels regardless of the preparation method. TCS was still microbiologically effective after the microwave process was applied. It was determined that microwave heating is a suitable method to obtain C974 organogels. This novel production technique developed might be promising especially in industrial scale when the dramatic reduction in the preparation time and energy were considered.

KEY WORDS: Carbopol; microwave; organogels; topical dermal delivery; triclosan.

INTRODUCTION

A gel may be defined as a semi-solid material constituted of gelator molecules at low concentrations (<15%). In the presence of a suitable solvent, these molecules form extensive mesh network preventing solvent flow as a result of surface tension (1).

Carbopols, which are very high molecular weight polymers of acrylic acid, have been used in producing pharmaceutical gel formulations widely (2). Carbopol gels are generally formulated in an aqueous solvent, and neutralization of the polymer ensures polymer hydration and a gel is formed. Usually, its acidic nature has been neutralized with a base-like triethanolamine to form strong gels (3). However, the addition of such a base is not always suitable for some drug substances, such as antioxidants. Moreover, the addition of water-insoluble drugs in such systems may cause non-homogeneous and non-transparent dispersions. As an alternative, hydrophilic water-miscible co-solvents can be used to produce formulations called organogels (1,4).

The organogels are bi-continuous systems made from gelators and apolar solvents. They do not always have water molecules captured within the self-assembled structures of the gelator. Especially in the field of dermal application, organogels have been investigated for the potential use as drug delivery systems (5).

Bonacucina *et al.* (2) recently prepared simple dispersions of Carbopols in different pure co-solvents like polyethylene glycol 400 (PEG 400) and glycerine by heating up to 70°C for 30 min, and according to rheological analysis, the best results were obtained with PEG 400. However, heating the system for 30 min is time and energy consuming. Therefore, in this study, microwave-assisted heating is offered as an alternative method for producing these kinds of gels. Microwave-assisted heating has several advantages like high efficiency, low energy consumption and homogeneity. Therefore, this method has been studied as energy source in almost all kinds of chemical reactions (6). It was reported that PNIPAM microgel could be prepared under microwave irradiation in a very short time with a yield of 98% (7). However, as to our knowledge, no detailed research has been conducted on the effect of microwave heating in producing Carbopol organogels.

The aim of this work was to prepare organogels of Carbopol 974P NF (C974) in PEG 400 avoiding long time heating and neutralization agents. A novel technique, high-speed homogenization followed by microwave heating was used. Triclosan (TCS) is used as a model drug (solubility in water, 10 μg/ml) (8). The organogels prepared by microwave heating have been compared with the organogels prepared by conventional heating. The rheological properties of the formulations have been evaluated. *In vitro* microbial efficacy and the accumulation of TCS in the rat skin have been investigated comparatively with a commercial product available in the market.

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MATERIALS AND METHODS

C974, PEG 400 and TCS have been purchased from Lubrizol (Belgium), Fluca (Italy) and Sigma Aldrich (UK), respectively. All other chemicals were of analytical grade.

Preparation of Gels

C974, at concentrations of 2%, 3% and 4%, was dispersed in 25 ml of PEG 400 separately, and the dispersion was homogenised (Ultra-Turrax Ika T25) for 5 min at 24,000 rpm.

Two methods of gel preparation were conducted on this homogenised dispersion. In the first method, the dispersion was heated at 80°C in a water bath under mechanic stirring at 200 rpm until a homogeneous and transparent system was formed (HT). In the second method, the dispersion was poured into glass Petri dishes and exposed to micro-irradiation (Arcelik MD574; 1,200 W/1 h) for 2 min, and spontaneously, a transparent system was formed (MW).

TCS was added to system (1% *w*/*w*) before homogenisation for drug-incorporated formulations (HT-TCS and MW-TCS).

Rheological Analysis

Rheological analysis was performed in triplicate using a thermostatically controlled rheometer (Haake Mars Modulars Advanced Rheometer Systems, Germany). The cone/plate geometry with 60 mm diameter and 1° angle was used, and the gap was 105 mm.

Oscillation stress sweep test was conducted for determination of the linear viscoelastic regime. Different ranges of stresses (0.05–10, 0.05–100 and 0.05–500 Pa) were applied to samples at a constant frequency of 1 Hz at 20°C. The shear strain, the stress and the phase angle were determined. The complex modulus, G^*, and the phase angle, δ, were obtained. The elastic modulus (G'), the viscous modulus (G'') and the dynamic viscosity ($\dot{\eta}$) were calculated using the following equations:

$$G^* = G' + iG'' \tag{1}$$

$$G' = G * \cos(\delta) \tag{2}$$

$$G'' = G * \sin(\delta) \tag{3}$$

$$\dot{\eta} = G''/\omega \tag{4}$$

The flow measurements were performed on the produced gels at the 0.05–10-Pa range of stress at 25°C. The obtained data was analyzed using the "power law":

$$\sigma = K\dot{\gamma}n \tag{5}$$

where σ is shear stress, K is consistency index, $\dot{\gamma}$ is shear rate and n is power law index.

The power law model gives $n=1$ and $K=1$, for a shear thinning (pseudo-plastic) fluid $n<1$ and for a shear thickening (dilatant) fluid $n>1$ for Newtonian samples.

Frequency sweep tests were conducted at 25°C with a step-wise increasing frequency range between 0.05 and 50 Hz frequency at 1 Pa stress, in the field of linear viscoelasticity.

Conductivimetry Studies

The electrical conductivity (σ) of PEG 400 and 1% TCS in PEG 400 was measured by using a conductometer (Jenway, 4071, Staffordshire, UK) equipped with a probe TetraCon 325, at 25±1°C. The tested material was placed in between two electrodes, and a potential was applied across the electrode. The current response was monitored as micro-Siemens per centimetre.

Differential Scanning Calorimetric (DSC) Analysis

DSC analysis was performed by a Perkin Elmer DSC 8000 to determine melting points and understand the crystallization behaviour. The samples were sealed in aluminium pans under nitrogen air atmosphere at a flow rate of 20 ml/min and evaluated in 25–150°C temperature ranges.

Proton Nuclear Magnetic Resonance (^{1}H-NMR)

NMR spectra for pure TCS and TCS extracted from gels were obtained on a Varian VNMRJ 400 nuclear magnetic resonance spectrometer. The reference used was 3-triisopropylsilyl propylsulphonate. Five milligrams of samples were diluted in 0.75 ml of solvent ($CDCl_3$), and the study was performed at room temperature.

Ex Vivo Studies

The abdominal skins of Wistar albino rats used in this study were supplied by University of Ege, Experimental Surgical Study Department. Hair on the dorsal side of the animals was removed with shaving razor in the direction of tail to head without damaging the skin. The shaven part of skin was separated from animals, and hypodermis including blood vessels was removed using surgical blade. The excised skin was washed with distilled water and subsequently used. The purified rat abdominal skin was mounted in Franz diffusion cells at 37°C, and 0.35 g of the formulations was placed on the skin. The formulations (4% MW-TCS and 4% HT-TCS) were kept in contact for 24 h, and at certain time intervals, TCS amount was determined in the samples taken from receptor phase (phosphate buffer solution, pH7.4). At the end of 24 h, the skin tissues were cleaned with a dry paper to remove the tested formulations, and they were homogenized with Ultra-Turrax at 8,000 rpm for 10 min. The accumulated TCS were extracted to 2 ml of ethanol during 24 h with the aid of a horizontal shaker (9). The samples were evaluated with a validated HPLC method (HP Agilent 1200) equipped with a UV detector set at 281 nm, using C18 column (250×4.6 mm; Waters, Alltech). The mobile phase consisting of acetonitrile:

water (90:10) was fluxed at 1 ml/min (10). The measurements were carried out for six samples per experiment.

Microbiological Efficacy Studies

Sabouraud's dextrose agar (Merck) was used for plate diffusion method for *Streptococcus aureus*. Petri dishes containing 20 ml medium were seeded with 100 µl of the bacterial inoculum. The plates were dried at room temperature for 15 min. Wells (1 cm in diameter) were cut out of the agar, and 100 mg of the formulations were placed. Gels without TCS were used to compare the inhibition zones as well. The plates were incubated for 48 h at 37°C, and the results were recorded by measuring the zones of growth inhibition. All data represent six separate experiments (11).

Statistical Analysis

Statistical analysis was conducted by one-way ANOVA followed by Tukey's multiple comparison test using target significance levels of 0.05 ($P<0.05$).

RESULTS AND DISCUSSION

Conventional heating is a successful method that is used to form Carbopol organogels (2,3). However, nowadays, microwave irradiation has been commonly used as an alternative heat source in pharmaceutical chemistry laboratories instead of conventional heating. The main advantage of microwave irradiation is the enhanced reaction rates. In case of a microwave heating, molecules exhibit a permanent dipole moment to align and perform certain movements such as rotation, friction and collision. These movements generate very fast heating in microwave absorbing solvents (12).

In the light of this knowledge, the target of this study was to prepare and evaluate Carbopol organogels using C974 in PEG 400 with the aid of microwave heating. C974 was preferred in terms of toxicological safety and ability of making higher amount of cross-links (13,14). C974 was homogenously mixed by Ultra-Turrax at 24,000 rpm before the formation of organogels, to ensure that C974 was dispersed in PEG 400 properly.

The rheological property of a semisolid drug carrier is a very important physical parameter for its percutaneous application (15). The physical appearances of semisolid formulations are affected from their viscoelastic properties that may alter the patient or consumer opinion (16). Viscoelastic properties also affect the contact times of gels that are related to bioavailability and therapeutic efficacy of the preparations (17,18).

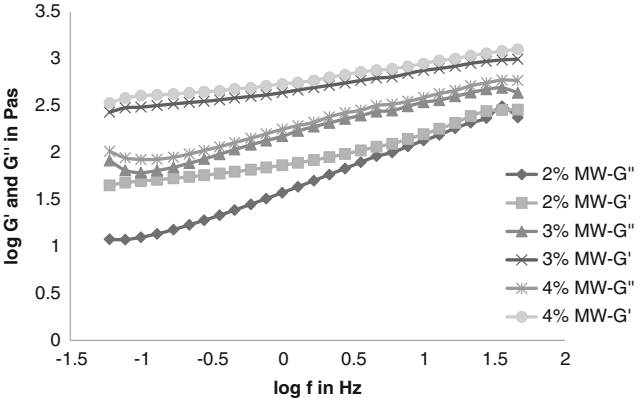


Fig. 2. Frequency sweep graphics of blank, 2–4% C974 organogels prepared with microwave-assisted heating (frequency, 1 Pa; hertz frequency range, 0.05–50 at 25°C)

The rheological experiments conducted in this study revealed that the blank gels prepared with 2% C974 were almost liquid dispersions, and the elastic modulus (G') value of the dispersions at the concentration of 2% C974 were not statistically different than the viscose modulus (G'') value. To name a structure as a gel, the elastic properties must dominate viscose properties ($G'>G''$) without being dependent on frequency (19–21). The viscous property was almost the same with the elastic property at the whole frequency range points for blank 2% C974 gels ($G''\approx G'$). The preparation method, neither conventional heating nor microwave-assisted heating, did not show a significant difference at this polymer concentration (Figs. 1 and 2). The formulations prepared with both method at 3% and 4% of C974 concentrations showed gel characteristics. As the concentrations of the polymer increased in PEG 400, the elastic properties also increased ($P<0.05$). These systems at the concentration of 3% and 4% showed a well-structured gel matrix behaviour instead of viscoelastic fluid behaviour. The elastic modulus G' was higher than viscose modulus G'' at most of the frequency range. The rheological behaviour of the gel structure was confirmed by the absence of frequency dependence.

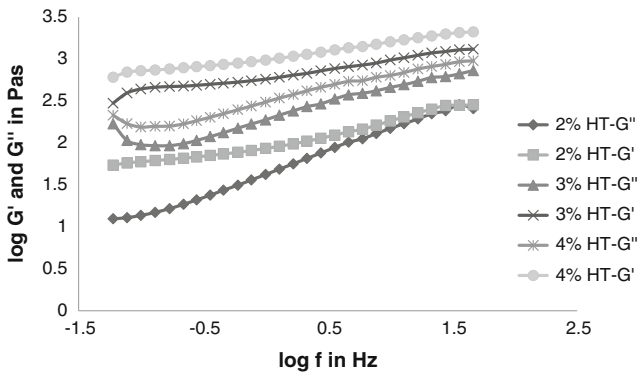


Fig. 1. Frequency sweep graphics of blank, 2–4% C974 organogels prepared with conventional heating at 80°C (frequency, 1 Pa; hertz frequency range, 0.05–50 at 25°C)

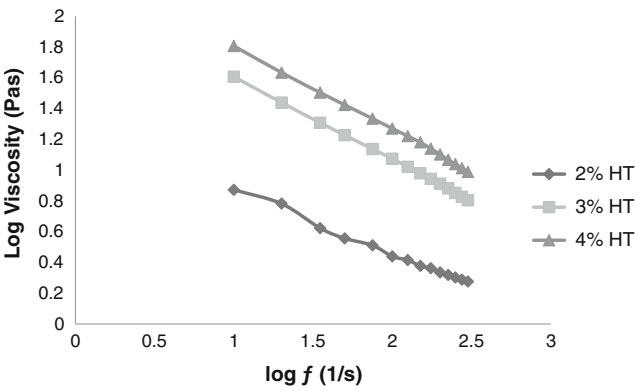


Fig. 3. Viscosity profile of blank, 2–4% C974 organogels prepared with conventional heating at 80°C

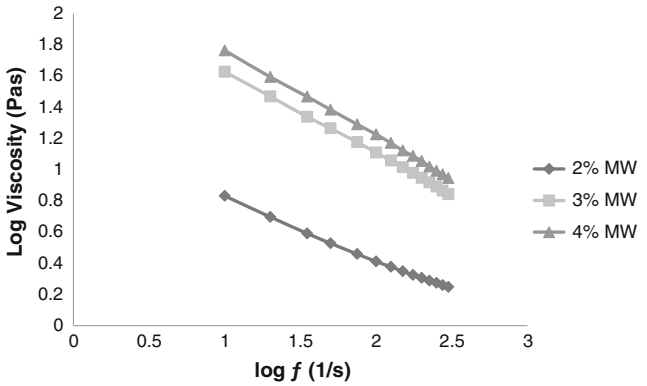


Fig. 4. Viscosity profile of blank, 2–4% C974 organogels prepared with microwave-assisted heating

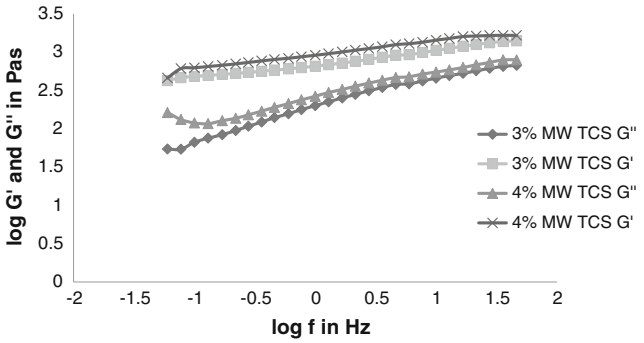


Fig. 6. Frequency sweep of TCS incorporated, 3% and 4% C974 organogels prepared with microwave-assisted heating

When two methods were compared in terms of the mechanical spectrum in the available frequency range, an increase in the sample elasticity and a greater predominance of the elastic character were observed with the gels prepared by conventional heat method especially for 3% and 4% of C974 concentration. Previously, the gelation properties of C974 were shown to be improved when there is a stronger polymer/solvent interaction such as solvation. It was reported that in conventional heating, polymer/solvent interactions proportionally decelerate polymer chain relaxation (3). Four percent MW gels performed nearly the same rheological characteristics with 3% HT gels (Figs. 1 and 2).

The interaction of microwaves with a material results in translational motions of free or bound charges and rotation of the dipoles. The resistances of these induced motions due to inertial, elastic and frictional forces cause losses in heating (22).

In prepared MW gels, the gelation completed very fast such as 2 min. At this time period, while C974 was solubilising, gelation was taking place at the same time, resulting in resistance for the transfer of heating. As a result of this phenomenon, it is very likely that a decrement in the solubilised C974 portion in PEG 400 will occur. Even though additional polymer amount was needed with microwave heating to obtain the same strength as conventional heated gels, the gels prepared by both methods were suitable for application at the same C974 concentration.

As can be seen from the viscosity profiles, the gels showed an elastic property at lower shear rates (Figs. 3 and 4). As the shear stress was increased, the gels started flowing. The viscosity profiles indicated a shear-thinning system for formulations of 3% and 4% of C974. Viscosity *vs*. shear rate on log–log plot (Figs. 3 and 4) followed power law behaviour. The graphics indicated that the gels resemble non-Newtonian fluids. As Barry and Meyer (23) stated, weakening of physical interacting points could be observed when the shear stress was high enough to disrupt the interactions. This kind of behaviour increases the spreadability of the gel when it is subjected to sustained high shear rates (24). At polymer concentration of 2%, the system resembled to viscous liquids, and as the polymer concentration increased in the system, the viscosity increased ($P<0.05$). The gels prepared with heat using C974 at 4% concentration were more viscous compared to gels prepared with microwave heating at the beginning of the experiment ($P<0.05$). However, this difference between methods could not be observed at 3% concentration. The gels obtained with both methods gave similar results when the shear was increased for all polymer concentrations.

Under the light of these data, it was decided that 2% of C974 amount was not enough for preparing a gel matrix with both methods. Hence, this concentration was excluded, TCS was incorporated into gel systems at C974 concentration of 3% and 4%, and additional frequency sweep tests were conducted.

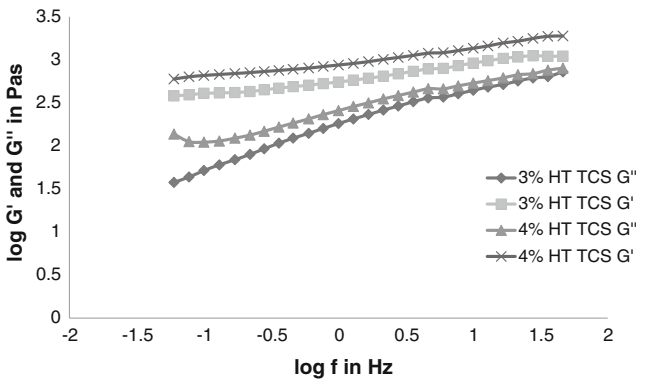


Fig. 5. Frequency sweep of TCS incorporated, 3% and 4% C974 organogels prepared with conventional heating at 80°C

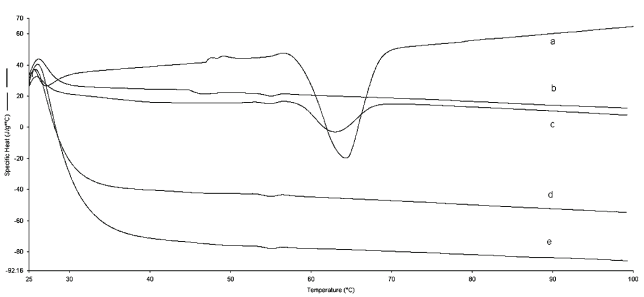
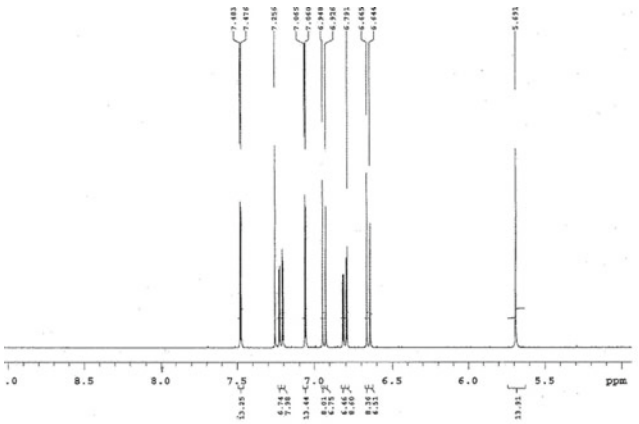
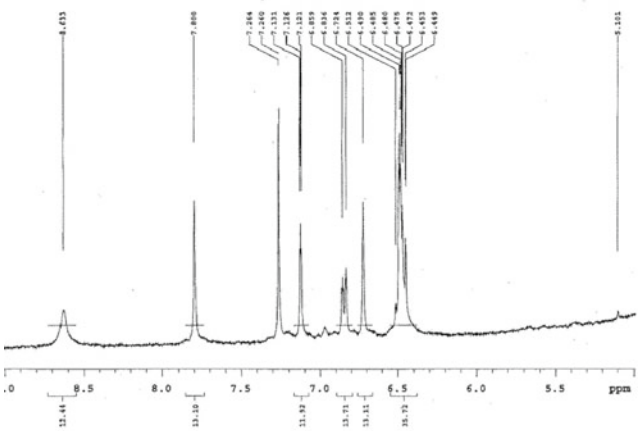


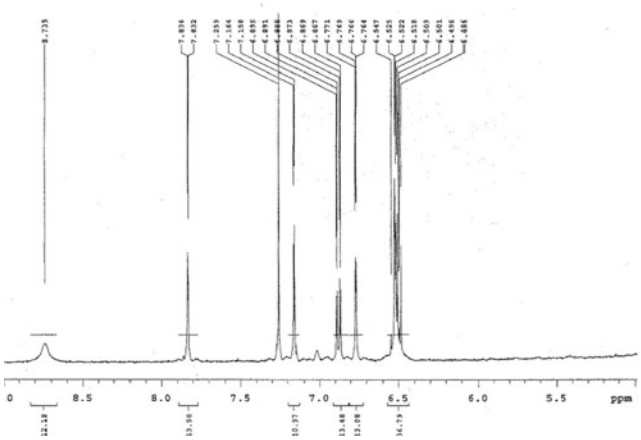
Fig. 7. DSC thermograms of *a* TCS, *b* C974, *c* physical mixture of TCS and C974, *d* 4% HT-TCS and *e* 4% MW-TCS obtained with a flow rate of nitrogen 20 ml/min at 25–150°C



Triclosan pure



Triclosan in MW Gel



Triclosan in HT Gel

Fig. 8. Proton nuclear magnetic resonance (^{1}H-NMR) data for pure TCS and TCS in organogels prepared with conventional heating and microwave heating

As can be seen from Figs. 5 and 6, when TCS was incorporated, the elastic modulus G' was still higher than viscose modulus G'' in a frequency-independent manner. The difference between the strength of gels obtained by two methods was not significant as it was in blank gels. These results revealed the presence of a stronger and more resistant structure, especially in those prepared with microwave heating. The addition of a drug with low aqueous solubility did not change the character but altered the strength of the gels prepared by microwave heating.

In microwave heating, the important phenomenon is volumetric heating. It differs from conventional heating due to the requirement of the diffusion from inside to the surface of the material. During volumetric heating, materials absorb microwave energy directly and internally and convert it to heat. This characteristic leads to rapid, controlled, selective and uniform heating (25). It has been stated that the changes in dielectric constant of the media might affect the gelation process (26).

It is known that dielectric constant of a material is related to electrical permittivity (27). To understand if TCS addition in PEG 400 had an effect of this parameter, conductivimetry studies have been carried out. The results indicated that there was a slight difference between PEG 400 and 1% TCS in PEG 400 solution. The data obtained were 2.2 and 2 μScm^{-1}, respectively. This difference was not dramatic; consequently, the distribution of heating might not be affected. However, the solubility of hydrophobic molecules may be increased by reducing the dielectric constant of the solvent. The solubility is a function of dielectric constant of polar and nonpolar medium. Most often, with hydrophobic materials, the solubility decreases with increasing dielectric constant (26). The slight decrement in conductivity by addition of TCS might have affected the solubility of C974 in PEG 400 leading to a better gel performance.

DSC analysis was conducted to understand if TCS was totally dissolved and materials were in crystallized state or not. DSC analysis is a helpful method for confirmation of the occurrence of crystallisation constitutes (28). Although it can be seen in the physical mixture of the polymer and the drug, the melting peak of TCS has disappeared in gel formulations prepared with both methods (Fig. 7). DSC data revealed that TCS was dissolved in PEG 400 during gel preparation.

NMR analysis was performed to provide information of the presence of TCS in the gels. The ^{1}H-NMR spectrum (Fig. 8) for the commercially available pure TCS provided seven signals (less the residual chloroform peak at 7.25 ppm) in or close to the aromatic region. The same signals were obtained from active substance in gels providing evidence that TCS was not affected from the preparation methods (29).

The diffusion and skin accumulation of TCS-incorporated gels (4% C974 prepared with both method) were analyzed comparatively with a commercial product, by ex vivo skin diffusion studies (30). The amount of TCS to be determined

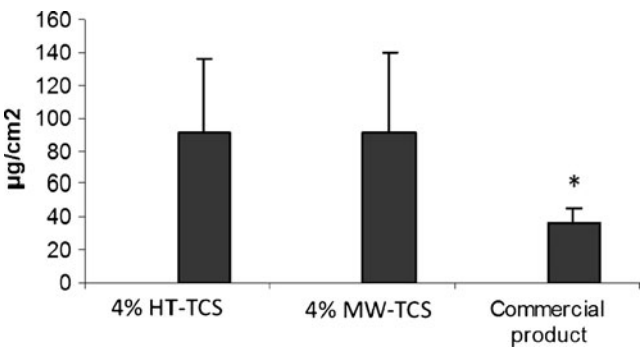


Fig. 9. The amount of TCS (micrograms per square centimetre) accumulated in rat abdominal skin delivered with 4% HT-TCS, 4% MW-TCS and commercial product. The results are the means of six samples per experiment, and the *bars* are ±SD. *$P<0.05$, commercial product *vs.* 4% HT-TCS and 4% MW-TCS

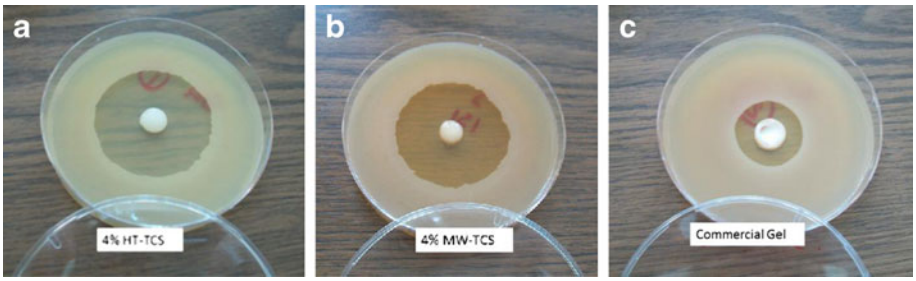


Fig. 10. Inhibition zones of *Streptococcus aureus in* Sabouraud's glucose agar plates obtained with TCS loaded gels: **a** 4% HT-TCS, **b** 4% MW-TCS and **c** commercial gel

from gels was checked before the experiment by HPLC to confirm that TCS amount was still stable in the formulations after the gelation process. After the validation of TCS amount in the gels, formulations were applied on the skin. TCS could not be detected in the receptor phase (PBS; pH7.4), even though the sink conditions were taken into account. There was no diffusion of TCS into the receptor phase of Franz diffusion cells. It was thought that the lipid/water partitioning of the drug might be effective on this result. Since log*P* of TCS was 4.8 (31), it was considered that its hydrophobic nature might result in the accumulation of TCS in the skin tissue. Therefore, the skin samples were homogenized, and the TCS accumulation was investigated (Fig. 9). The accumulation of TCS in the skin did not show a significant difference in terms of gel preparation method. On the contrary, skin accumulation ability of TCS had been improved by these novel organogels regardless of the preparation method.

To understand if the drug was still active after the gelation process, microbiological studies were conducted. TCS is used as an antibacterial agent in dermal products against acne vulgaris, which is thought to be caused primarily by *S. aureus* (10,32). Mean zone of inhibition (mm±SD) could be listed in order as:

$$4\%\ \mathrm{MW{-}TCS}_{(45\pm0.76)} \approx 4\%\ \mathrm{HT{-}TCS}_{(45\pm0.57)} > \text{Commercial gel}_{(40\pm0.57)} > \text{TCS suspension}_{(15\pm1)} > 4\%\ \mathrm{MW}_{(0,\ \text{no effect})} = 4\%\ \mathrm{HT}_{(0,\ \text{no effect})}$$

The microbiological studies revealed that the formulations were effective, and this antimicrobial effect was significantly greater than TCS suspension in water and commercial product but the same for both organogels (Fig. 10).

CONCLUSION

The organogels of C974 in PEG 400 by high-speed homogenization followed by microwave-assisted heating was successfully prepared for the first time in this study. The strength of the produced organogels was polymer concentration dependent. Two percent of C974 concentration failed to form a gel structure with both methods applied. Three percent and 4% of C974 in PEG 400 formed gel structures that were characterized by an elastic property greater than viscose property ($G'>G''$). High lipophilicity of TCS was an advantage for the solubilisation in organic solvents, and no crystallization occurred in produced organogels. TCS was not affected from the microwaves, and its structure has not been changed by microwave irradiation. TCS was microbiologically effective after the microwave process was applied. The skin accumulation of TCS from organogels was better than the commercially available product. Microwave-heated and conventionally heated organogels prepared at 4% of polymer concentration showed the same skin accumulation and microbiological efficacy.

As a conclusion, it can be stated that microwave heating is a promising method to obtain C974 organogels with appropriate characteristics. This novel production technique developed might be beneficial, especially in industrial scale when the dramatic reduction in the preparation time and energy were considered.

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Conflicts of interest The authors declare no conflict of interest in this manuscript.

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