doi.org/10.36721/PJPS.2022.35.4.SP.1215-1221.1

Physicochemical, rheological and antifungal evaluation of miconazole nitrate organogels for topical delivery

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Abstract: Topical preparations have a problem of being wiped off after a short time, which results in low activity of the active moiety. In this research, topical organogels (OGs) were prepared with different oils for the controlled action of miconazole nitrate. Various oils were checked for their gel-forming ability. Controlled release OGs were prepared with a 15% concentration of glyceryl monostearate. Differential scanning calorimetry was performed to study the thermal behavior of gels. X-ray diffraction revealed that the drug was changed into an amorphous form from the crystalline form. The absence of any interaction between the active ingredient and excipients was concluded by Fourier Transform Infrared spectroscopy. Permeability studies were carried out with cellulose acetate membrane by using Franz diffusion cell containing phosphate buffer saline pH 7.4. The release of drug followed the Weibull model. A frequency sweep test was performed to study the rheological behavior of optimized formulations. Rheology revealed the true nature of formulations whether they are gels or just viscous fluids. Images of scanning electron microscopy showed a network formed by the gelator molecules. The antifungal activity was checked against C. albicans and A. niger and it was best by the formulation made by TT. It was concluded that all the OGs gave controlled topical antifungal action.

Keywords: Controlled release, gelator, oils, organogels, topical preparation, antifungal activity

INTRODUCTION

Among many species of organisms that cause infections, fungi cause endemic and severe infections mainly in the immunocompromised and incapacitated host (Carmona and Limper, 2017). Mycosis, the fungal infection of the skin, is broadly classified into superficial and subcutaneous infection, categorized on the basis of the depth of skin involved in infection. Superficial cutaneous mycoses include dermatomycosis and subcutaneous infections include chromoblastomycosis (Kalus, 2017). Miconazole nitrate (MN) has a broad spectrum of activity against fungus and is effective against vulvovaginitis and cutaneous candidiasis caused by C. albicans. The design of a dosage form that allows controlled release of the drug and ensures prolonged retention of the drug over the skin surface will improve the anti-fungal prowess of MN against many fungal infections of the skin.

For most of the topical pharmaceutical preparations, local action is required on the skin with minimal absorption and prolonged contact with the skin. For local action of drugs, the most commonly used formulations are ointments, creams, pastes and gels, solid dry powders, aerosol sprays and organogels (OGs) (Mayba and Gooderham, 2018). The OGs are defined as bi-continuous systems consisting of gelators and apolar solvent, which may or may not contain water molecules entrapped within the self-assembled structures of the gelator. An OG is considered a semi-solid preparation with viscoelastic properties. Its external phase is immobilized and apolar and becomes non-flowing inside spaces present in three dimensional meshes like structure formed by the physical interactions in between the self-assembling structures of gelators (Esposito *et al.*, 2018).

When the gelators are added, there may be chemical or physical interactions in order to make self-assembled fibrous like structures that entangle with one another. It results in the development of a structure consisting of 3D network. The 3D network structure does not allow the flow of apolar phase (Shakeel *et al.*, 2021). Fatty acid derived sorbitan OGs are made of non-ionic hydrophobic molecules and exhibit surface active properties capable of immobilizing a variety of solvents including vegetable oils and isopropyl myristate. The gel formation does not include water so they are resistant to microbial growth. The gels formed by incorporating such gelators are thermoreversible and opaque. They exhibit thermal stability at room temperature even for weeks (Cerqueira *et al.*, 2017).

Plant-derived oils possess a lot of medicinal properties and have been frequently used against the microbial infections as these oils are rich in active constituents (Álvarez-Martínez *et al.*, 2021). Delivery of these bioactive oils is quite troublesome due to their inherent hydrophobic nature and loss of the volatile components. There is a need to develop a suitable carrier for simultaneous loading of the natural oils and the antimicrobial drugs to increase the overall killing of the

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microbes and reduce the incidence of antimicrobial drug-resistance. In this study, we report the use of glycerol monostearate (GMS) as an organogelator to immobilize the therapeutically active natural oils along with the antifungal drug, miconazole nitrate (MN).

MATERIALS AND METHODS

Materials

Miconazole nitrate (MN) was a gift from Valor Pharmaceuticals, Islamabad, Pakistan. Glyceryl monostearate (GMS) was obtained from China. Lemon grass oil, clove oil and tea tree oil were purchased from Qarshi Industries (Pvt.) Ltd., Pakistan. Lemon citrus oil and black seed oil were purely extracted from plant parts. Methanol and Tween 80 were purchased from Daejung Company, Ltd. Korea. Potassium dihydrogen phosphate (KH_2PO_4) was purchased from Duksan Reagents, Korea. Sodium hydroxide pellets (NaOH) were obtained from SIGMA Aldrich, Germany. Hydrochloric acid (HCl) was obtained from MERCK (Germany). Distilled water was obtained from Pharmaceutics Research lab, Government College University, Faisalabad. Strains of Aspergillus niger and Candida albicans for antifungal assay were obtained from Drug testing Laboratory, Faisalabad, Pakistan.

Preparation of OGs

Different oils were tested in this study as Lemon grass oil (LG), Lemon citrus oil (LC), Tea tree oil (TT), Black seed oil (BS) and Clove oil (CL). GMS was used as a gelating agent. For this purpose, measured quantity of GMS was melted in a beaker at a controlled temperature (70^{o}C). Then, measured quantity of oil was added and the GMS dispersed well in the oil (sol state). After complete dispersion, the sol state was cooled with continuous stirring at 150rpm. The gel was formed upon cooling (gel state). In order to obtain medicated OGs, the drug was dispersed in the sol state and it was cooled to form the OG.

Organoleptic Characterization of OGs

The OGs were physically examined for color, texture, phase separation and greasiness. Small quantity (100mg) of each formulation was pressed between fingers to observe consistency and checked whether any coarse particle stick to fingers or not. 100mg gel was applied on the backside of the hand and rubbed gently. The layer was washed with tap water after drying it and noticed whether it is washable or not. The pH of plain and medicated OGs was determined by pH meter (H1 2210 Hanna, United states) at 25^{o}C±0.5. The pH meter electrode was immersed into the gel and the readings noted.

Spreadability of plain and medicated OGs was determined by pressing the sample between the two plates. Two glass plates of almost equal weight were taken; 0.2g gel was weighed in the lower plate and the upper plate was placed over it without moving the plates. Initial diameter of the gel was noted. Then, the gel was pressed by placing 200g and 500g weight and the diameter was noted after 1 minute. Spreadability was determined by following formula: Spreadability = D_2/D_1

Gel-sol transition temperatures were determined by using test-tube inversion method. Optimized formulations were placed in the test tubes and all the test tubes were placed in a water-bath having controlled temperature. The temperature of water-bath was changed from 35^{o}C to 80^{o}C. The temperature was gradually increased with a difference of 5^{o}C after every 5 minutes. At each temperature, after waiting for 5 minutes, the tubes were inverted and the gels were observed whether they started flowing or not. The temperature was noted at which they started to flow; this is gel-sol transition temperature.

Drug Content

For drug content determination, 250mg of OG was taken in 10mL volumetric flask. Small quantity of methanol was added, vortexed and the volume made up with the solvent. The dilution was vortexed and filtered with 0.22µm syringe filter. Dilutions were analyzed spectrophotometrically at 272nm. The concentration of drug was found by calibration curve and drug content was determined with the help of the following formula:

$$\text{Drug content} = \frac{\text{Actual concentration}}{\text{Theoretical concentration}} \times 100$$

FTIR, DSC, XRD and SEM

Samples were analyzed by FTIR over the range of 4000-650cm^{-1} at 4cm^{-1} resolution to study the interaction of excipients with the drug.

DSC of optimized medicated formulations was performed on DSC-TGA Standard SDT Q600 V20.9 Build 20. 25mg of each sample was placed onto the sample holder and the samples were studied between the temperature range of 34-250^{o}C at a heating rate of 5^{o}C/min. The graphs obtained from samples were compared with that of drug's DSC graph.

XRD of optimized formulations was performed by using Cu-Ka as the X- ray source, operated at 35kV and 30mA. The OGs were scanned in the range of 5^o–50^o 2θ at a scanning rate of 2^{o}2θ/min.

The OGs visualization by SEM (VEGA3 TE SCAN) was carried out by first converting them into xerogels under vacuum and then sputter-coating with gold. Images were taken at different magnifications to reveal the true morphology of the gels.

Drug Release

Using Franz diffusion cell, OGs were studied for drug release at different intervals up to 24 hours using

phosphate buffer saline pH 7.4 and tween 80 was used to maintain sink condition as MN is insoluble in buffer. The temperature was maintained at 32°C. Samples were analyzed by UV-spectrophotometer.

Rheology

Rheology studies were carried out by using Rotary rheometer RHEOTEST RN 5.1. Frequency sweep test was carried out between the frequency range of 0.1 and 50Hz at 1Pa stress, by using plate 1 of instrument with the diameter 60mm, gap adjustment 0.5mm and filling capacity 0.509ml. Frequency sweep was done to study the viscoelasticity of OGs. The analysis provided the information about changes in storage modulus (G') and loss modulus (G") as the frequency of given stress is changed.

Antifungal Assay

The medicated OGs were checked for their antifungal activity against C. albicans and A. niger. Sabouraud dextrose agar was used as media for fungi. The culture was evenly spread onto the plates. Extra volume of culture was drained out. Then the wells were made with sterile borer. 150mg of each gel was placed into each well. Then the plates were incubated at 37°C for 7 days. After 7 days, zone of inhibition was measured.

STATISTICAL ANALYSIS

Statistical comparison of the dissolution profiles was made by F2-similartity index using DDSolver. One way-ANOVA was employed where necessary using GraphPad Prism, and significance was considered at p-value < 0.05.

RESULTS

Preparations of OGs and CGC determination

All the oils were tested for gel formation ability. Gels were not prepared with clove and lemon citrus oils because GMS could not immobilize these liquids. The quantity of GMS to form OGs was determined for all the oils. Critical gel concentration (CGC) depends on the nature of the oil. The OGs were formulated with LG, TT and BS oils at a minimum 10% GMS concentration. Below this concentration, the gel is not made because the concentration of GMS is low in order to properly immobilize the oil molecules. So, CGC for LG, TT and BS oils was 10% of GMS.

Organoleptic Characterization of OGs

Gels with LG, TT and BS oils were prepared at different concentrations of GMS. All the gels passed the inverted tube test. 10% gels were made but started to flow upon little stirring. 15% gels were accurate as they did not flow and did not become hard. 20% gels were hard. Hence, 15% gels were optimized for further study. All the OGs had characteristic color of their respective oils, such as LG gels showed white color; BS gels had sharp orange-yellow color; and the TT gels showed light yellow color. All the prepared OGs were smooth and homogeneous. They did not show any coarse particles. The BS gels were smoother and had slight shinny appearance as compared to the other gels. This was due to specific nature of BS oil to give luster. All the formulations at and above CGC did not show any phase separation. They were stable even after three months. All the formulations were homogenous and greasy in nature because of the presence of oil and showed no coarse particles. Formulations were difficult to be washed completely with water because of oily nature.

It was noted that as the concentration of GMS increased, pH of formulation also increased because of its basic nature (Kenechukwu *et al.*, 2018). The pH slightly dropped down with the addition of MN as shown in fig. 2. The normal pH range of skin tissues is 4.1 to 5.8 (Proksch, 2018) and the prepared OGs conform to this criterion. As shown in fig. 3, the spreadability of the formulations decreased with increase in the gelator concentration; as the strong network did not allow the molecules of formulation to spread more easily. So, spreadability was found to be gelator-concentration dependent. The nature of oil also affected the spreadability as the denser oil showed less spreadability. Spreadability was enhanced when higher weight was placed on the upper plate, as increase in stress causes mobility of molecules indicating the property of OGs to become more mobile in increased stress. The temperature at which the gels started flowing was in the range of 70-75°C. It was 70°C for L2P, L2M, T2P and T2M; and 75°C for B2P and B2M. OGs with BS required more temperature to lose their gel characteristics. This indicated stronger network in the BS based OGs than the OGs of other oils.

Drug Content

The drug content was determined spectrophotometrically and the results are displayed in fig. 4. All the formulations showed a promising drug content >95%.

Table 1: Composition of OGs with different oils

Formulation code	GMS	Oil	Drug
L1P	10%	90% (LG)	-
L2P	15%	85% (LG)	-
L3P	20%	80% (LG)	-
L2M	15%	83% (LG)	2%
T1P	10%	90% (TT)	-
T2P	15%	85% (TT)	-
T3P	20%	80% (TT)	-
T2M	15%	83% (TT)	2%
B1P	10%	90% (BS)	-
B2P	15%	85% (BS)	-
B3P	20%	80% (BS)	-
B2M	15%	83% (BS)	2%

FTIR, DSC, XRD and SEM

Fig. 5 shows the FTIR spectra of the GMS, oils and the respective OGs. GMS showed sharp peaks around 1500 and 3000cm^{-1}. The peaks at 2981cm^{-1} in the spectra of GMS indicated the presence of alkyl group, whereas a sharp peak at about 1740cm^{-1} hinted towards the presence of ester group (Ghan *et al.*, 2020). The medicated formulations contain only 2% MN and 98% rest of the excipients so many peaks are merged in FTIR spectra. However, spectra of medicated formulations differ from that of plain ones because of the presence of some specific peaks at different wavenumbers as they showed some specific peaks at 800cm^{-1}. This is because of the presence of C-Cl in MN as alkyl halide functional group shows peaks between 600 and 800cm^{-1}. The peaks around 1000cm^{-1} specifically present in medicated formulations are due to the presence of ether; as ether shows specific peaks between 1000 and 1300cm^{-1}. The hydroxyl group of nitric acid in MN showed specific peaks between 2500 and 3300cm^{-1}. Amine group showed specific peaks between 3300 and 3500cm^{-1}. The spectra also showed specific peaks of aliphatic C–H stretching (2,960cm^{-1}) and aromatic C–H stretching (3,048cm^{-1}) (Qushawy *et al.*, 2018).

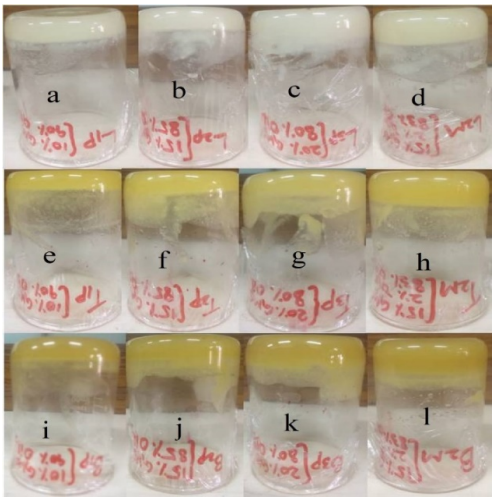

Fig. 1: Physical appearance of (a) L1P, (b) L2P, (c) L3P, (d) L2M, (e) T1P, (f) T2P, (g) T3P, (h) T2M, (i) B1P, (j) B2P, (k) B3P and (l) B2M

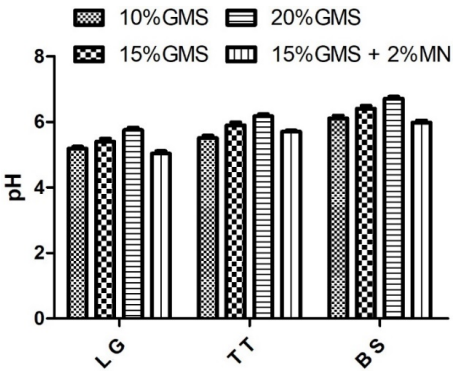

Fig. 2: pH of different OGs

DSC results in fig. 6 show a sharp peak at 199^{o}C indicating the melting point of MN. However, the drug was completely dispersed in all preparations as evident by the absence of the peculiar endothermic peak of drug in OGs.

XRD studies (fig. 7) showed specific peaks of MN according to its crystalline behavior in pure form. None of the formulations showed any such crystallization behavior.

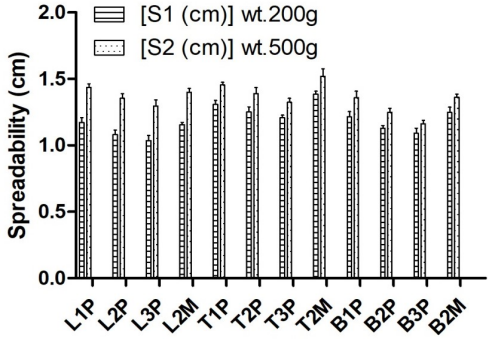

Fig. 3: Spreadability of different OGs

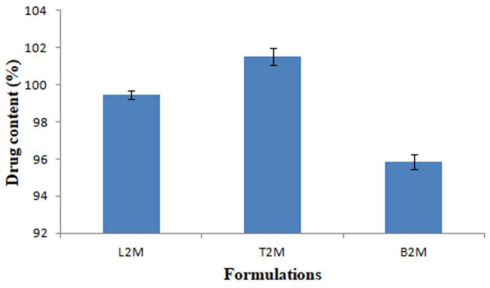

Fig. 4: Drug content of different OGs

Morphology of the OGs (fig. 8) highlighted the fibrous structures in the framework of OG 3D network, whereas, the pure drug showed well-defined crystalline structure. The absence of the crystals of drugs in the matrix of the OGs strengthen the observations from solid-state characterization studies that the drug was molecularly embedded in the OG network.

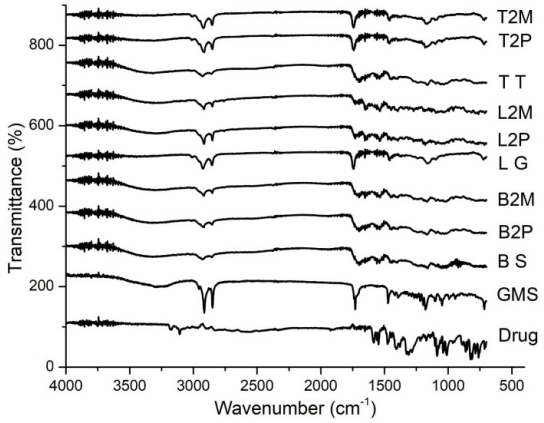

Fig. 5: FTIR of drug, GMS, oils, and different OGs

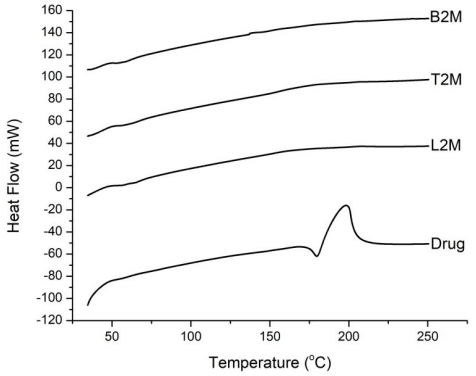

Fig. 6: DSC of drug and different OGs

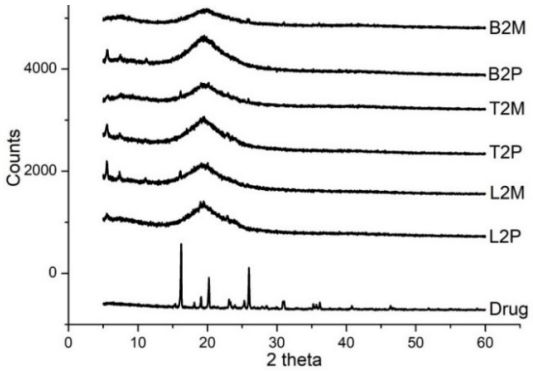

Fig. 7: XRD of drug and different OGs

Drug Release

The drug release results (fig. 9) showed that most of the drug remained on skin for topical action as antifungal therapy. Only 15% drug was released even after 24 hours hence, major portion of the drug was available on the skin for action. Different models (zero-order, first-order, Higuchi and Weibull) were applied on the release data of OGs. The highest R^2 and least AIC values were obtained with Weibull model (table 2). Dissolution profile comparison by DDSolver revealed similar drug release profiles on the basis of value of F2-similarity factor greater than 50.

Rheology

Frequency sweep test showed that storage modulus was higher than the loss modulus for most of the frequency range as shown in fig. 10. L2P gave very smooth graph for G' and G" and G'>G" at whole frequency range. So, it shows true behavior of gels. For L2M G'>G", it gave oscillations at some frequency range indicating multiple relaxation processes. G" was greater than G' for T2P up to 30 1/s frequency and later on G'>G". So, T2P behaves as a viscous fluid up to 30 1/s frequency and after that behaves as a gel. But, as a whole, it was not a gel but a high viscous fluid. T2M behaved as a gel for whole frequency range but gave oscillations. B2P behaved as a viscous fluid up to frequency 39 1/s and later on, behaved as a gel as G'>G". B2M also performed as a viscous fluid up to frequency 37 1/s and as a gel later on.

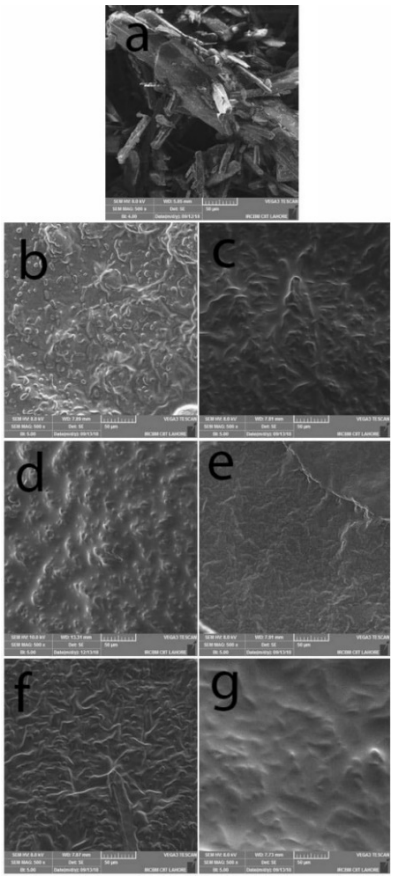

Fig. 8: SEM images of (a) Drug (b) L2P (c) L2M (d) T2P (e) T2M (f) B2P (g) B2M

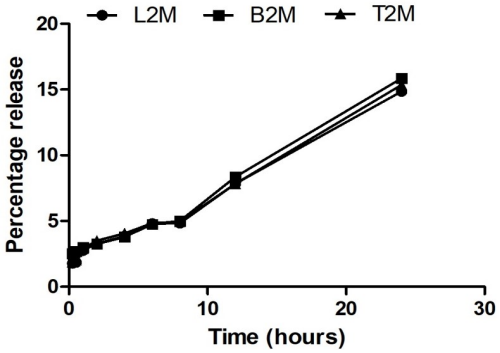

Fig. 9: Drug release from medicated OGs

Table 2: Kinetics of drug release from different OGS

Model	Criterion	L2M	B2M	T2M
Zero order kinetics	R2	0.87	0.84	0.86
	AIC	27.21	29.91	28.43
First order kinetics	R2	0.88	0.85	0.87
	AIC	26.46	29.40	27.79
Higuchi model	R2	0.88	0.84	0.87
	AIC	26.85	30.17	27.95
Weibull model	R2	0.99	0.99	0.99
	AIC	7.74	4.57	8.09
	β	1.52	2.19	1.78

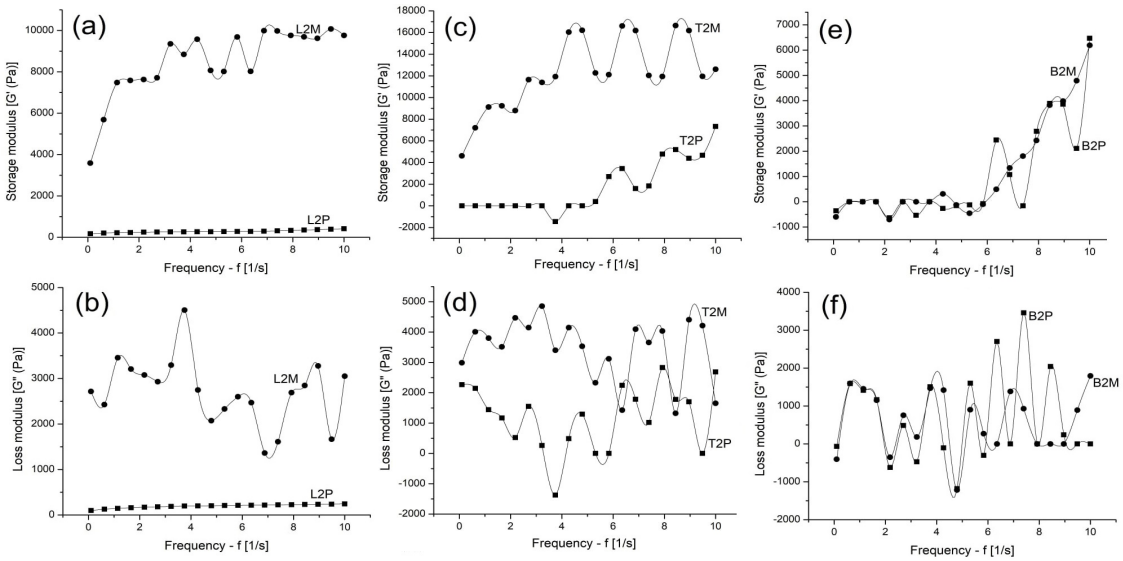

Fig. 10: Rheology graphs of optimized formulations comparing Storage and Loss modulus

Antifungal Activity

The zone of inhibition was calculated after 7 days of incubation. As shown in fig. 11, all the formulations behaved differently against *C. albicans* and *A. nigar*. But there was significant difference among formulations' behavior against *A. nigar*. T2M showed the highest zone of inhibition for *A. niger*, whereas L2M showed less activity against *A. niger*. All three medicated organogels showed good activity against *C. albicans*.

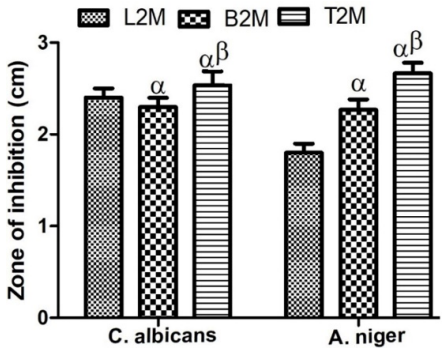

Fig. 11: Zone of inhibition of medicated formulations, p-value <0.05 was considered significant; α shows significant difference against L2M, β shows significant difference against T2M

DISCUSSIONS

LG, TT and BS oils formed OGs at specific concentration of GMS. The failure of gel formation occurred for clove oil and lemon citrus oil due to the highly volatile nature of the oils. As the bonding between the molecules of the oils itself was not strong, so the energy of molecules was high, hence GMS was not able to immobilize the molecules of these oils. However, no phase separation was observed for the OGs made from LG, BS and TT oils, which showed that GMS held the molecules of liquid strongly and built strong 3D network that prevented oil separation (Zheng *et al.*, 2016). This dense network might be due to the apolar-aploar interactions among the gelator and the oils. These hydrophobic interactions among the gelator molecules and the oils define the stability of the OGs. This strong network is the reason f absence of syneresis even after long time storage. DSC and XRD studies revealed the absence of the sharp melting peak of MN and the loss of crystallinity, respectively, pointing to the molecular dispersion of the MN within the matrix of OGs (Dai *et al.*, 2020, Vigato *et al.*, 2019). As observed by SEM, the assembly of the OGs appeared to be in the form of fibrous 3D network and has been reported previously (Li *et al.*, 2018).

Weibull equation expresses the accumulated fraction of the drug in specific time. The dissolution never ends in this model and there is always infinitely small amount of undissolved substance left (Kosmidis and Macheras, 2018). The shape parameter, β, characterizes the curve as either exponential (β=1), S-shaped with upward curvature followed by a turning point (β>1), or as one with a steeper initial slope and is then made consistent with the exponential (β<1). All three formulations showed β values higher than 1 so the curves were almost S-shape with upward curvature.

The gels usually have greater storage modulus (G') than loss modulus (G") without depending upon the frequency (de Francisco *et al.*, 2019). Rheological studies showed that the addition of the drug increased storage modulus, hence increasing the elasticity of the formulations.

L2P, L2M and T2M acted as gels, while T2P, B2P and B2M behaved as viscous fluids. Except L2P, all the formulations showed oscillatory behavior as they showed multiple relaxations. The difference in the antifungal activity of the medicated OGs was because of the activity of individual oil and the penetration ability of the drug

from each formulation into the agar. The more the drug released, the larger the zone of inhibition noted. Moreover, the TT is well known for its superior antifungal activity (Francisconi *et al.*, 2020). Hence, T2M showed higher antifungal activity due to the combined effect of TT and MN.

CONCLUSION

GMS OGs were prepared successfully with lemon-grass oil, tea-tree oil and black-seed oil at 15% GMS without any syneresis. 3D network of the optimized formulations was revealed in SEM images. DSC and XRD results revealed a loss of crystallinity of the drug. Drug release behavior indicated suitability of the OGs for topical delivery of MN as the drug was released slowly for controlled action. Hence, the MN was homogenously mixed with oil and gelator, thus providing easy, smooth and equal application of the drug on the skin. The antifungal assay indicated comparatively good activity of TT containing OGs against *C. albicans* and *A. niger*.

ACKNOWLEDGEMENTS

Authors acknowledge the financial support provided by Higher Education Commission, Pakistan for conducting the research.

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