There are two challenges in vaginal drug delivery. First, the limited contact time caused by the physiological conditions imposed by the protective mechanisms of the vagina (resulting in a frequent dosing regimen). The second challenge is patient compliance. Conventional vaginal dosage forms such as ointments and inserts cause discomfort to the patients (1). Although it is known that patients tolerate gels better than inserts or ointments, direct application of gels into the vagina might be difficult as well as inconvenient (1). Recently, in situ gelling liquids have been investigated as a more convenient

The purpose of this study was to develop pluronic-based in situ gelling formulations of metronidazole (MTZ) for treatment of bacterial vaginosis, aimed at prolonging the residence time, controlling drug release, enhancing efficacy, decreasing recurrence, and increasing patient compliance. The in situ gel formulations were prepared using different concentrations of pluronic F-127 (PF-127) alone and in combination with pluronic F-68 (PF-68). The prepared formulations were evaluated for their gelation temperature (T\text{gel}), in vitro drug release, rheological properties, mucoadhesion properties and tolerability by vaginal mucosa in tissue levels. The T\text{gel} decreased with increasing PF-127 concentration. The T\text{gel} was modulated by addition of PF-68 to be within the acceptable range of 25–37 °C. With increasing pluronic concentration, the in vitro drug release decreased, viscosity and mucoadhesive force increased. Histopathological examination of rabbit vaginas from the control and treated groups revealed normal histology of the vagina and cervix. Based on the in vitro evaluation of prepared formulations, the in situ gelling liquid formulated with PF-127/PF-68 (20/10 %, m/m) was selected for further clinical evaluation.

**Keywords:** metronidazole, in situ gelling, mucoadhesion, pluronics

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dosage form for topical applications. The in situ forming hydrogels are stimuli-sensitive hydrogels that exist as aqueous solutions before administration and immediately change into standing gels after administration upon contact with the mucosa. The most commonly used thermoreversible gels are pluronics (2). The pluronic-based in situ gelling dosage form is supposed to be easily applied and to give good spreading and coating of the vagina, making the treatment more effective and probably result in prolonged effect (1, 3).

Metronidazole (MTZ) was considered a drug of choice for treatment of bacterial vaginosis. Prolonged treatment was found to be the only effective solution to prevent the high recurrence rate; however, such approach raises concerns about potential toxicity.

The objective of this study was to design a new vaginal thermosensitive in situ gelling formulation with mucoadhesive properties.

EXPERIMENTAL

Materials

Metronidazole was generously donated by Nile Pharmaceuticals and Chemical Industries Co. (Egypt). Pluronic F-127, Pluronic F-68, mucin powder and benzalkonium chloride were purchased from Sigma Chemical Co. (USA). Sodium chloride, calcium hydroxide, potassium hydroxide, acetic acid, and glycerol were obtained from El-Nasr Company (Egypt). All the other chemicals were of pharmaceutical grade and were used as received. The marketed preparation Tricho® 0.75 % (commercial MTZ vaginal gel) was purchased from Chemical Industries Development (CID) Co., Egypt.

Preparation of pluronic gel formulations

Different concentrations of Pluronic F-127 alone or in combination with Pluronic F-68 were used in the preparation of in situ gelling liquids. Medicated in situ gelling liquids were prepared on a mass basis using the modified cold method (4). Composition of the prepared formulations is shown in Table I. For formulations F1 to F8, Pluronic F-127 or combination of Pluronic F-127 and Pluronic F-68 were mixed and dissolved with 0.8 % MTZ in cold citro-phosphate buffer of pH 4.5. Benzalkonium chloride, concentration 0.01 %, was used as preservative. Partially dissolved pluronic solutions were stored in a refrigerator at 4 °C overnight and stirred periodically until clear homogenous solutions were obtained.

Gelation temperature \( (T_{gel}) \) measurement

Ten milliliters of cold sample solution (pluronic containing formula) were put into a beaker (25 mL) placed in a low temperature water bath at room temperature. A thermometer was immersed in the sample solution. The solution was heated at a constant rate of 200 rpm under continuous stirring using a magnetic bar (Barnstead/Thermolyne, USA). The temperature at which the magnetic bar stopped moving due to gelation was reported as the gelation temperature \( (T_{gel}) \) (5). Each sample was measured in triplicate.
Rheological studies

Rheological studies of the samples were carried out using a DV-III Ultra viscometer, RV model, Brookfield, USA. Viscosity was measured at different temperatures of 4, 25 and 34 °C. The viscosity of each sample was determined before and after gelifying. Each point is the mean of three readings.

Mucoadhesive force determination

Mucoadhesive forces of all the prepared formulations were determined using a mucoadhesive force measuring device, which is a modified balance. This balance was developed in our laboratory with slight modifications, according to the previously reported methods (6).

The mucoadhesive force of the formulations under examination was determined by measuring the force required to detach the formulation from a mucin disc using the measuring device. At the right arm of the balance, a mucin disc was horizontally glued to the lower surface of the right pan of the modified balance. The mucin disc was hydrated with distilled water prior to the mucoadhesion test. Three drops of each formula were placed on the upper surface of an inverted beaker, which was placed directly below the right pan. The in situ forming liquid sample was exposed to a source of heat to allow gelation. The upper stage of the modified balance containing the hydrated mucin disc was adjusted to be in contact with the preparation. A preload of 10 grams was immediately applied for 1 minute to ensure intimate contact between the mucin disc and the sample and to allow formation of an adhesive bond. The preload time and the force were kept constant for all the tested formulations. After completion of the preload time, water was allowed to drip from the infusion set into a preweighed plastic jar placed on the left pan of the balance at a constant rate of 5 mL per minute. The dripping of water was stopped when the mucin disc was detached from the tested sample, the filled plastic jar was reweighed and the mass of water required to detach the tested sample from the mucin disc was calculated from the difference (7).

Measurements were repeated three times for each of the gel preparations, but a fresh smooth gel surface was created before each measurement.

In vitro release of MTZ from in situ gelling formulations

In vitro release of MTZ from in situ gelling formulations was studied using a standard semi-permeable cellophane membrane. The release medium was a simulated vaginal fluid (SVF). Simulated vaginal fluid was prepared as described (8). The pH of the mixture was then adjusted to 4.5 using HCl. The membrane was firmly stretched over one end of the glass tube (2.4 cm internal diameter) by means of a rubber band. One gram of the tested formulation solution was weighed over the membrane in the dialysis tube. The tube was suspended in a 250-mL glass cup containing 100 mL freshly prepared release medium (SVF) (9). The experiment was carried out at constant temperature in a shaking water bath previously adjusted to 37 ± 0.2 °C and 75 stroke per minute. Aliquots (1 mL) were withdrawn from the release medium at each sampling time for up to 6 h and 24 h in case of comparison with the marketed preparation. The aliquots were re-
placed with an equal volume of the freshly prepared release medium kept at the same
temperature. The aliquots were diluted, and the amount of drug released was calculated
by measuring the absorbance at 320 nm against a blank (UV spectrophotometer, Jenway,
UK). The results were the mean of three runs. The release profile of MTZ was obtained
by plotting the % cumulative amount of drug released from each formulation against
time.

Histopathological study of vaginal tissues

Formula selection was done by screening all prepared formulations through the in
vitro histopathological characterization (10) for their tolerability by vaginal tissues. The
study obtained the approval from the Ethical Committee of the Faculty of Pharmacy,
Assiut University. Five adult female rabbits (weighing 1.5–2 kg) were used. F7 muco-
adhesive thermosensitive formulation was administered into the vagina (1 mL kg⁻¹) for
three consecutive days. At 6 h post last dose, specimens from vagina and cervix were
isolated and fixed in 10 % neutral buffer formalin, dehydrated in a graded alcohol series,
cleared with methyl benzoate and embedded in paraffin wax. Four micron sections were
cut and stained with haematoxylin and eosin (HE) for histopathological examination by
light microscopy. Specimens from control rabbits (no gel administered to the vagina),
were similarly treated for comparison.

RESULTS AND DISCUSSION

MTZ concentration in all formulations was 0.8 % m/m and that of pluronic varied
0–30 % (Table I). Drug content uniformity of the prepared formulations ranged from 99.2
to 100.3 % of the labeled amount.

Gelation temperature (T_gel)

T_gel is the temperature at which the liquid phase makes a transition to gel. An ideal
in situ gel should be a free flowing liquid at room temperature so as to allow reproduc-
ible administration into the site of application where it undergoes in situ phase transition
to form a strong gel (11). The human vaginal temperature is 37.2 °C (12), so T_gel of vagi-
nal thermoreversible gels were considered to be suitable if they were in the range of
25–37 °C. If the T_gel is lower than 25 °C, a gel might be formed at room temperature,
leading to difficulties in manufacturing, handling, and administering. If T_gel is higher
than 37 °C, a liquid dosage form still exists at vaginal temperature, resulting in drainage
of the formula from the vagina at an early stage.

The data in Table I show that PF-127 alone at concentrations of 15, 20, 25 and 30 %
(F1–F4) gave T_gel higher than 40, 22, 18 and 10 °C, respectively. These gelation tempera-
tures are not within the suitable range. An increase in PF-127 concentration resulted in a
decrease in T_gel, this finding was in agreement with the data of Edsman et al. (13).

A modulation of T_gel to reach the desired range was achieved by using a combina-
tion of the two pluronics (grades F-127 and F-68).
Effect of PF-68 addition on $T_{gel}$. – $T_{gel}$ for PF-127 solutions and the solutions of PF-127/PF-68 mixtures are shown in Table I. Formulations F5–F8 were found to gel between 25 and 37 °C, so they were considered to be suitable for vaginal application. Several combinations of the two polymeric grades were tested and used in the formulation of the in situ gelling liquids in order to select formulations having a suitable $T_{gel}$ (Table II). As shown in Tables I and II, the $T_{gel}$ changed with the addition of PF-68 to 15 and 20 % PF-127. The results showed that at constant PF-127 concentration, increasing the PF-68 concentration gradually increased the $T_{gel}$ initially to a maximum, and then it decreased. Maximum concentration of PF-68 was 10 %. $T_{gel}$ decreased with further increment in PF-68 concentration. Similar results were previously reported (14).

Table I. Composition of pluronic-based vaginal in situ gelling formulations of MTZ and their gelation temperatures

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Ingredient (%, m/m)$^{a,b}$</th>
<th>$T_{gel}$ (°C)$^{c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>15 PF-127, 0 PF-68</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>F2</td>
<td>20 PF-127, 0 PF-68</td>
<td>22 ± 0</td>
</tr>
<tr>
<td>F3</td>
<td>25 PF-127, 0 PF-68</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>F4</td>
<td>30 PF-127, 0 PF-68</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>F5</td>
<td>15 PF-127, 15 PF-68</td>
<td>36 ± 1</td>
</tr>
<tr>
<td>F6</td>
<td>15 PF-127, 20 PF-68</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>F7</td>
<td>20 PF-127, 10 PF-68</td>
<td>28 ± 0</td>
</tr>
<tr>
<td>F8</td>
<td>20 PF-127, 15 PF-68</td>
<td>27 ± 1</td>
</tr>
</tbody>
</table>

$^{a}$ Vehicle: citrate-phosphate buffer pH 4.5.

$^{b}$ MTZ content in all formulations 0.8 % (m/m); content uniformity 99.2–100.3 %.

$^{c}$ Each value represents the mean ± SD of three experiments.

Table II. Effect of PF-68 on gelation temperature

<table>
<thead>
<tr>
<th>PF-127 (15 %)</th>
<th>PF-127 (20 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-68 (%)</td>
<td>$T_{gel}$ (°C)$^{a}$</td>
</tr>
<tr>
<td>0</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>10</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>15</td>
<td>36 ± 1</td>
</tr>
<tr>
<td>20</td>
<td>29 ± 1</td>
</tr>
</tbody>
</table>

$^{a}$ Each value represents the mean ± SD of three experiments.
It is known that when the concentration and temperature of the polymer are above a critical value, pluronic molecules in aqueous solution will self-assemble to form spherical micelles with a dehydrated polypropylene oxide (PPO) core surrounded by hydrated swollen polyethylene oxide (PEO) chains (15). The thermoreversible gelation behavior is accepted as a result of micellar entanglement and packing with the increase in temperature. Furthermore, it is generally accepted that the PPO, which is hydrophobic, has lowered $T_{gel}$ and the PEO, which is hydrophilic, has increased $T_{gel}$. Therefore, a different PEO/PPO ratio will lead to a different $T_{gel}$. The ratio of PEO/PPO in PF-127 is 7:3, while in PF-68 it is 8:2. Thus, when a slight amount of PF-68 is added to a PF-127 solution, the proportion of PEO increases, which leads to an increase in $T_{gel}$ (11, 14). The possible reason for $T_{gel}$ decrease after a certain concentration of PF-68 (10 %) is that the incorporation of a small amount of PF-68 can only change the PEO/PPO ratio, causing an increase in $T_{gel}$, while by increasing the PF-68 concentration sequentially, not only the PEO/PPO ratio changes, but also the micellization of PF-68 molecules can participate in the construction of the gel, which finally leads to a decrease in $T_{gel}$ (14).

**Rheological study**

Rheological behavior is the key part in the formulation of PF-127 preparations. Table III shows the viscosity of pluronic formulations at different PF-127 concentrations. The same concentration of pluronic has different viscosity at different temperatures (4, 25, and 37 °C), where the viscosity increased with increasing temperature. This may be attributed to the fact that pluronics, being non-ionic PPO triblock copolymers, aggregate into micelles at 37 °C. This micellization is due to the dehydration of polymer blocks with temperature. It has been shown that gel formation is a result of micellar enlargement and packing and that the gel is more entangled at higher PF-127 concentrations. As a result of these micelle entanglements, they cannot separate easily from each other, which accounts for the rigidity and high viscosity of gels containing high concentrations of pluronics (15, 16).

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Viscosity (mPa s) at temperature</th>
<th>Mean mucoadhesive force $\times 10^2$ (N cm$^{-2}$)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 °C</td>
<td>25 °C</td>
</tr>
<tr>
<td>F1</td>
<td>0.00</td>
<td>66.7</td>
</tr>
<tr>
<td>F2</td>
<td>&lt; 100</td>
<td>138.3 $\times 10^3$</td>
</tr>
<tr>
<td>F3</td>
<td>233</td>
<td>151.5 $\times 10^3$</td>
</tr>
<tr>
<td>F4</td>
<td>280</td>
<td>170 $\times 10^3$</td>
</tr>
<tr>
<td>F5</td>
<td>333.3</td>
<td>916.4</td>
</tr>
<tr>
<td>F6</td>
<td>333</td>
<td>1.677 $\times 10^3$</td>
</tr>
<tr>
<td>F7</td>
<td>306</td>
<td>932</td>
</tr>
<tr>
<td>F8</td>
<td>422</td>
<td>1.177 $\times 10^3$</td>
</tr>
</tbody>
</table>

$^a$ Mean ± SD, $n = 3$.

$^b$ Gelation temperature of F1 was > 40 °C, so it could not be handled during mucoadhesive force determination (it liquefied during the experiment).
Effect of PF-68 addition on viscosity. – Table III shows the results for the viscosity of PF-127 formulations containing PF-68. Formulations composed of PF-127/PF-68 at concentrations 15/15 (%) (F5), 15/20 (%) (F6), 20/10 (%) (F7) and 20/15 (%) (F8) showed the effect of PF-68 concentration on viscosity. The four formulations were liquid at 4 and 25 °C. At 4 °C, the four formulations did not show any notable change in viscosity. At 25 °C, formulation 15/20 (%) (F6) showed 1.8-fold higher viscosity compared to 15/15 (%) (F5), but formulation 20/15 (%) (F8) showed 1.3-fold higher viscosity compared to formulation 20/10 (%) (F7) at 25 °C. At 37 °C, formulations 15/20 (%) (F6) and 20/15 (%) (F8) showed 14.4- and 1.1-fold higher viscosity than the other formulations, respectively. This is attributed to the fact that the thickening power of pluronics in water increased with the hydrophobic molecular mass and the ethylene oxide/propylene oxide ratios (17).

Mucoadhesive force determination

Mucoadhesive force is an important and crucial physicochemical parameter for in situ forming vaginal gels since it prevents the formulation from rapid drainage and hence prolongs its residence time. Results of the determination of mucoadhesive forces of all the formulations are collected in Table III. This table shows that the prepared MTZ in situ gelling formulations with PF-127 possessed satisfactory adhesive properties. Increasing the mucoadhesive polymer concentration significantly increased the mucoadhesive force. Similar results were previously reported (18). The mucoadhesion rank order for PF-127 formulations was 20 < 25 < 30 %.

Addition of PF-68, which is a homologene of PF-127, enhanced the bioadhesive force, since the pluronic with a hydrophilic oxide group could bind to oligosaccharide chains. The higher the concentration of PF-68, the greater the bioadhesive force of pluronic gels.

In vitro release of MTZ from in situ gelling formulations

Fig. 1 shows the cumulative amount of MTZ released vs. time profiles for various drug-containing polymer solutions and the drug solution (control). All the polymer solutions and the control contained 0.8 % (m/m) MTZ. For the drug solution, more than 90 % of MTZ was released after 1.5 h.

To study the effect of PF-127 concentration on drug release, the release of MTZ from different PF-127 concentrations was investigated. Drug concentration (0.8 %, m/m) and the temperature 37 ± 0.2 °C were kept constant, while the PF-127 concentration was varied (20, 25 and 30 %). The results show that as the concentration of PF-127 increased from 20 to 30 %, the amount of drug released decreased. This indicates that the structure of the gel functioned as an increasingly resistant barrier to drug release as the concentration of PF-127 increased. Such enhanced resistance may be due to the reduction in the number and dimension of water channels and to the increase in the number and size of micelles within the gel structure. Shorter intermicellar distance leads to a larger number of cross-links between neighboring micelles, leading to higher viscosity and lower rate of drug release (19). This assumption may be potentiated by the rheology study. From the rheological study, it was observed that there is an inversely proportional relationship between MTZ viscosity and release rate.
Effect of PF-68 on the release rate

To study the effect of PF-68 on the release rate of MTZ from the pluronic-based in situ gelling formulations, a release test was performed using the formulations composed of a constant concentration of PF-127 (15 or 20 %, m/m) and variable concentrations of PF-68. PF-68 showed little effect on the release rate of MTZ from in situ gelling formulations. As shown in Fig. 1, the addition of 20 % PF-68 to 15 % PF-127 (F₆) resulted in a slight decrease in the release rate compared to 15 % PF-68 (F₅). In case of 20 % PF-127, the addition of 10 % (F₇) and 15 % PF-68 (F₈) showed a very low reduction in the release rate. This slight decrease in the release rate may be attributed to the increase in viscosity.

The formula suggested for clinical study was F₇ based on Tgel, which was considered an important parameter. The formulations with suitable Tgel were F₅, F₆, F₇, and F₈. The rank order for drug release was F₅ > F₆ > F₇ ≥ F₈. Thus, the final choice between F₇ and F₈ depended on the viscosity, mucoadhesion and the total concentration of the two pluronics. Table IV shows that the difference between F₇ and F₈ regarding viscosity and mucoadhesion was very small. Either of the two formulations could be used, so the formula that contained smaller concentration of pluronic (20/10 %) was recommended (F₇). F₇ was easier to be prepared than F₈.

![Fig. 1. Effect of concentrations of PF-127 alone and PF-127/PF-68 combinations on the release profile of MTZ from in situ gelling formulations (SEM bars, n = 3).](image-url)

**Table IV. Viscosity and mucoadhesion difference between F₇, F₈ and Tricho® gel**

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Viscosity (mPa s)</th>
<th>Bioadhesive force × 10² (N cm⁻²)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 °C</td>
<td>25 °C</td>
</tr>
<tr>
<td>F₇</td>
<td>306</td>
<td>932</td>
</tr>
<tr>
<td>F₈</td>
<td>422</td>
<td>1177.7</td>
</tr>
<tr>
<td>Tricho® gel</td>
<td>153.5 × 10³</td>
<td>156 × 10³</td>
</tr>
</tbody>
</table>

ᵃ Mean ± SD, n = 3.
Histopathological study of vaginal tissues

Histopathological examinations from the control group and from the treated group (after using formulation F7) revealed normal histology of the vagina and cervix (Fig. 2). It was reported that thermosensitive gel vehicles, which were composed mainly of pluronic (PF-127 and PF-68), did not influence the viability of the cells and did not alter the morphology of vaginal tissues, i.e., there was no visible sign of inflammation or necrosis (1).

Comparison of MTZ release from the selected in situ gelling formula (F7) and the marketed gel (Tricho® gel)

We compared our formula to the marketed formulation already in use regarding sustained release, viscosity and mucoadhesion as the basis for our clinical study.

It was found that the release from MTZ in situ gelling formulation F7 was slower than that from the marketed gel (Tricho® gel). After 6 h, the percent drug released from Tricho® gel was 91 %, while the percentage released from F7 was 76 % (Fig. 3a). Fig. 3b shows that the drug was completely released from Tricho® gel after 12 h, while 90 % MTZ was released from F7 after the same period. These in vitro results suggest that plu-
ronic formulations might serve as a rate-controlling barrier and can be useful as a vehicle for sustained release preparations of MTZ.

The differences between formulation F7 and Tricho® gel in viscosity and mucoadhesion are summarized in Table IV. Viscosity of Tricho® gel did not change with temperature increase. In contrast to Tricho® gel, the free flowing property of formula F7 would enable the patient to apply the required dose accurately and would result in good spreading and coating of the vagina. At 37 °C, the viscosity of F7 was higher than that of Tricho® gel. Table IV shows that the mucoadhesion expressed as detachment force of formula F7 and Tricho® gel were 0.2116 and 0.1133 N cm⁻², respectively. Based on these results, it is expected that formula F7 will be retained on vaginal mucosal tissue for a longer period than the Tricho® gel.

Clinical evaluation of formula F7 in comparison with the marketed preparation (Tricho® gel) in patients with bacterial vaginosis (20) showed that the cure rate after one week of treatment was 85 % in the in situ gel F7 group and 71 % in the conventional vaginal gel group (Tricho® gel), while after 4 weeks, the cure rate showed a significant difference in the in situ gel group compared to the conventional vaginal gel group (80 versus 47 %, respectively, p = 0.034). This shows that the in situ MTZ vaginal gel F7 is more effective than the conventional vaginal gel product for sustained cure of bacterial vaginosis.

**CONCLUSIONS**

The in situ gelling liquids are considered a more convenient formulation for topical application into the vagina. Formula F7 was the most suitable of pluronic formulations. It showed appropriate viscosity, mucoadhesion, delayed release and $T_{gel}$ within the suitable range. From the release and mucoadhesion studies, it was found that the in situ gel formula will be retained in the vagina for a longer period than Tricho® gel. Histopatho-
logical examination of vaginal and cervical sections from the control and MTZ treated groups revealed normal histology. Hence, the use of this formulation is expected to make the treatment more effective as it gives good spreading and coating properties of the vagina, which was confirmed by the clinical study conducted later on.

REFERENCES


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**SAŽETAK**

**Razvoj i karakterizacija *in situ* gelirajućih pripravaka metronidazola na bazi pluronika za vaginalnu primjenu**

EL-SAYED ALI IBRAHIM, SAYED ISMAIL, GIHAN FETIH, OMAR SHAABAN, KHALED HASSANEIN i NOURA HASSAN ABDELLAH

Cilj rada bio je razviti pripravke metronidazola (MTZ) za liječenje bakterijske vaginoze koji imaju sposobnost geliranja *in situ*, prodižujemo vrijeme zadržavanja na mjestu primjene, kontrolirano oslobađanje ljekovite tvari, povećanu učinkovitost te smanjiti ponovnu pojavu vaginoze i povećati suradnju pacijenta. Pripravci koji geliraju *in situ* pripravljeni su koristeći različite koncentracije pluronika F-127 (PF-127), samog ili u kombinaciji s pluronikom F-68 (PF-68). Ispitivana je temperatura geliranja ($T_{gel}$) formulacija, *in vitro* oslobađanje ljekovite tvari, reološka svojstva, mukoadhezijska svojstva te kako ih podnaša vaginalna sluznica u slojevima tkiva. Uočeno je da se s povećanjem koncentracije PF-127 snažava $T_{gel}$. Dodatkom različitih količina PF-68 dobiveni su pripravci s rasponom $T_{gel}$ od 25 do 37 ºC. S povećanjem koncentracije pluronika smanjilo se oslobađanje ljekovite tvari *in vitro*, a povećala se viskoznost i mukoadhezivnost. Histopatološka ispitivanja na zečicama ispitivane i kontrolne skupine dala su normalni histopatološki nalazi njihovih vagina i cerviksa. Na temelju *in vitro* evaluacije, formulacija s PF-127/ PF-68 (20/10 %, m/m) izabrana je za daljnja klinička ispitivanja.

**Ključne riječi:** metronidazol, *in situ* geliranje, mukoadhezija, pluronici

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