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Development of Formulations for Vaginal Gel Carrier in the Pharmacy - a Regulatory and Quality Aspect

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SUMMARY

On the basis of the *Law on Medicines and Medical Devices of the Republic of Serbia*, a magistral medicine means a medicine prepared in the pharmacy according to a prescription (formula) for an individual patient - user. In practice, the more need is for *ex tempore* production of vaginal preparations in the pharmacy and galenic laboratory. Due to the small number of registered vaginal gel products on the world market, and even less on our own market, their production in the pharmacies is very important.

The aim of this study was to examine the possibilities of development the vaginal gel carriers with different hydrophilic polymers, in the pharmacy, in accordance with the requirements of the European Pharmacopoeia. For their production we used three different mediums for gelation: Carbopol® 940, Carbopol® Ultrez 10 and Pemulen® TR 1 NF.

All formulations show similar organoleptic properties during the observed period of time. Measured pH values of carrier formulations do not differ significantly compared to the normal pH values of vaginal fluid. Optimal value for viscosity has a formulation A_1 (formulation with Carbopol® 940), thus that formulation is our recommendation for the development of vaginal gel carrier. Because of the complicated procedure of registration of the generic drug, recommended formulation for vaginal gel carrier, as magistral medicine, has a great importance for patients who require precise adjustment of therapy.

Key words: **magistral medicine, carrier, vaginal hydrogel, legislation, viscosity**

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INTRODUCTION

On the basis of the *Law on Medicines and Medical Devices of the Republic of Serbia* (Article 24 paragraph 13), a magistral medicine means a medicine prepared in the pharmacy according to a prescription (formula) for an individual patient - user. A galenic medicine means a medicine prepared based on the current pharmacopea or based on the current magistral formulae in the galenic laboratory, which is intended for the patients - users of the pharmacy or other medical institution (1).

Regulations on the galenic drugs used in human medicine ("Official Gazette of RS", No. 85/2011) in the part *List of galenic medicinal products used in human medicine*, lists ***Metronidazoli mucilago vaginalis 0.75%***, which is based on the current magistral formulae of the Republic of Serbia (MF2008, chapter *Vaginalia - Semi-solid vaginal preparations*).

In Sixth European Pharmacopoeia (Ph. Eur. 6.0) in its general part we can find the monograph of vaginal preparations (*Vaginalia*). Vaginal preparations are liquid, semi-solid or solid preparations intended for administration to the vagina usually in order to obtain a local effect. They contain one or more active substances in a suitable carriers (basis).

Several categories of vaginal preparations may be distinguished (pessaries, vaginal tablets, vaginal capsules, vaginal solutions, emulsions and suspensions, tablets for vaginal solutions and suspensions, semi-solid vaginal preparations, vaginal foams, medicated vaginal tampons) (2).

Semi-solid vaginal preparations are ointments, creams or gels. They are often supplied in single-dose containers. The container is provided with a suitable applicator. Semi-solid vaginal preparations comply with the requirements of the monograph *Semi-solid preparations for cutaneous application* (2).

Ph. Eur. 6.0 provides all the requirements for quality and legislation which is necessary for the product to comply:

- Uniformity of dosage units (liquid and semi-solid single-dose vaginal preparations);
- Uniformity of content (solid single-dose vaginal preparations with a content of active substance less than 2 mg or less than 2 per cent of the total mass);
- Uniformity of mass (solid single-dose vaginal preparations);
- *Dissolution test* (demonstrate the appropriate release of the active substance(s) from solid single-dose vaginal preparations);
- Containers for semi-solid preparations for cutaneous application comply with the requirements for *Materials used for the manufacture of containers* and *Containers*;
- A test method for judging the preservative properties of the formulation are provided in *Efficacy of antimicrobial preservation*;
- *Microbiological quality of pharmaceutical preparations* - Category 2;
- Sterile semi-solid preparations are prepared using materials recommendations provided in *Methods of preparation of sterile products* (2).

In practice, the more need is for *ex tempore* production of vaginal preparations in the pharmacy and galenic laboratory. Creams and gels are commonly used for vaginal administration because of the better release of the active substance. Spreading of creams and gels over the vaginal mucosa is better than with other semi-solid forms, as they can be easily mixed with vaginal fluid. Creams and gels can be applied by using the applicator, or can be spread to the diaphragm (3).

Vaginal gels are often the basis for spermicides (nonoxynol-9), metronidazole, progesterone, inductors of childbirth, antifungals, antiseptics, antiphlogistics, lactic acid, but they are also used as an "empty" gels for moisturizing of dry vaginal mucosa (4).

To ensure good therapeutic effect it is necessary to provide an appropriate carrier (base) of the vaginal gel, easy application and its prolonged contact with mucous membrane (5).

The composition and physico-chemical properties of vaginal gel carriers affect the bioavailability of the active substance (6). Carrier must be inert, physically and chemically stable, non-toxic, odorless, compatible with medicinal substances which are incorporated into the gel. Also, it should not cause irritation or sensitization on the application site, or to slow down the course of treatment (4).

It is difficult to define the ideal value of the viscosity of vaginal gels. The ideal vaginal gels should possess an excellent ability to cover the vaginal mucosa, together with adequate retention feature which allows retention of the formulation *in situ*. Several factors affect the viscosity of vaginal gels. First of all there are composition of gels, temperature (especially important for thermolabile gels), vaginal pH value, fluid that can be found in the vagina (vaginal fluid, semen) and others. Temperature, pH value and interactions with fluids present in the vagina might cause the changes in viscosity, which should be taken into account when formulations are designed. It was found that small variations in gel composition lead to changes in its viscosity (7).

In current literature and in practice there is a very small number of studies related to the development of semi-solid carriers for vaginal preparations in the pharmacy. Development of new polymeric materials - gelling agents, which are used to produce hydrogels for topical application provides the opportunity to explore them in the formulations for vaginal use. Due to the small number of registered vaginal gel products on the world market, and even less on our own market, their production in the pharmacies is very important.

In our country, only vaginal gel with progesterone 8% is registered (**Crinone®**, Fleet Laboratories Ltd., UK) (8).

AIM

The aim of this study was to examine the possibilities for development of vaginal gel carriers with different hydrophilic polymers, in the pharmacy, in accordance with the requirements of the European Pharmacopoeia.

MATERIALS AND METHODS

In this study, we used the following materials and reagents:

- Carbopol® 940 (2-propenoic acid homopolymer or poly(acrylic acid), Noveon, USA);
- Carbopol® Ultrez 10 (a cross-linked poly(acrylic acid), Noveon, USA);
- Pemulen® TR 1 NF (2-methylbutanoic acid homopolymer, Noveon, USA);
- Propylene glycol (Ph. Eur. 6);
- Sodium hydroxide (Ph. Jug. IV);
- Disodium edetate (Ph. Jug. IV);
- *Pulvis conservans* (a mixture of the methylhydroxybenzoate and propylhydroxybenzoate 2+1, Ph. Jug. IV);
- Acetonitrile (Lichro Solv®, Reag. Ph. Eur., Merck);
- Sodium dihydrogen phosphate (Ph. Jug. V);
- Phosphoric acid, concentrated (Ph. Eur. 6);
- Standard buffer solutions for pH meter calibration (pH=4.1 i pH=7.1);
- Purified water (Ph. Jug. V);
- Deionized water (conductivity of 0.055 μS cm-1).

In this study we used the following instruments:

- Laboratory scales PCB 2000-2B KERN & Sohn GmbH, Germany;
- Column electronic mixer RW 16 basic IKA® - WERKE;
- Microprocessor pH Meter HANNA Instruments;
- Rotating viscometer Visco Basic Plus, Fungilab.

All of the three formulations were made using the same procedure, at room temperature. For their production we used three different mediums of gelation: Carbopol® 940, Carbopol® Ultrez 10 and Pemulen® TR 1 NF (Table 1).

Disodium edetate is dissolved in a certain volume of purified water (70 ml). *Pulvis conservans* is dissolved in propylene glycol and the mixture is added to an aqueous solution of disodium edetate. The polymer is disperged in that solution. Dispersion is made by mixing with the laboratory mixer at 700 r/m (in order to avoid the collapse of polymer gel structure, which is resulting in loss of viscosity of the Carbopol® gel) (9). The resulting dispersion is opalescent, with no lumps. The solution of sodium hydroxide 10% (18 drops) (10) is added to the dispersion and mixing is continued until the homogeneous gel was formed.

Figure 1. *Column electronic mixer RW 16 basic IKA® - WERKE*

The samples were packed in plastic containers and stored in tightly closed containers, protected from light, at room temperature (20±5°C).

Table 1. *The formulations for vaginal gel carriers*

Constituents	Formulation (g)		
	A_1	A_2	A_3
Carbopol® 940	1,00	-	-
Carbopol® Ultrez 10	-	1,00	-
Pemulen® TR 1	-		1,00
Dinatrii edetas	0,10	0,10	0,10
Propylenglycolum	10,0	10,0	10,0
Natrii hydroxydi solutio 10%	1,00	1,00	1,00
Pulvis conservans	0,10	0,10	0,10
Aqua purificata	ad 100,00	ad 100,00	ad 100,00

Examination of the organoleptic properties

In this study we observed the following organoleptic characteristics of gel carriers: appearance, color, odor, homogeneity, easiness of application, adhesiveness, sensibility on the skin after application, transparency, appearance of the film which formulation leaves on the skin.

Easiness of application, adhesiveness and appearance of the film were studied by applying carrier on the skin, while the other characteristics were determinated visually.

Samples were observed 24h, 15 days and 30 days after their production. Samples were kept in plastic containers, protected from light, at room temperature (20±5°C).

Determination of pH

pH value of the carrier is a very important parameter for the development of vaginal gels. Since the physiological pH range in the vagina is 3.8 to 4.2, it is desirable that the pH value of preparation is in that range. Stability of the constituents at a particular pH value is very important. Ph. Eur. 6.0 gives a description of the method of potentiometric determination of pH in the *General chapters*, *Methods of analysis* (*Physical and physicochemical methods*).

Determination of pH of samples was made by direct immersion of the pH meter electrode in the sample (as these are hydrogels with high water content). The measurements were performed at a temperature of 21.7 °C, with the previous device calibration with standard buffer solutions (pH=7.1 and pH=4.1).

Figure 2. *Microprocessor pH Meter HANNA instruments and standard buffer solutions for pH meter calibration (pH=4.1 i pH=7.1)*

Three measurements of pH value were made for each sample (the whole quantity of gel is divided into three parts, which are packed in plastic containers, in order to examine the possible impact of packaging on the pH value). Measurements were performed 24h, 15 days and 30 days after sample production.

Determination of viscosity

The viscosity of samples was determined by rotating viscometer *Visco Basic Plus*, *Fungilab*.

Figure 3. *Rotating viscometer Visco Basic Plus, Fungilab*

Ph. Eur. 6.0 in the *General chapters*, *Methods of analysis*, describes the method for determining the viscosity using the rotating viscometer. The principle of the method is to measure the force acting on a rotor when it rotates at a constant rotational speed in the formulation. The dynamic viscosity is measured. The unit of dynamic viscosity is the pascal second (Pa·s). The most commonly used submultiple is the millipascal second - mPa·s.

We measured the changes in viscosity of gel carriers depending on the number of revolutions per minute (RPM values). In this case, RPM can have values from 0.3 to 100. The measurements were performed at 22°C. We used the spindle with the label R6 (number six refers to the diameter of the spindle).

Determining the viscosity of samples was performed on the following values of RPM: 100, 60, 50, 30, 20, 12, 10, 6, 5, 4, 3, 2.5, 2, 1.5, 1, 0.6. The highest accuracy was obtained at 4 rpm (45.7%). 45.7% indicates the percentage of the maximum value that the device can measure with a defined spindle and number of revolutions and then the measured value is the nearest to the value of 50% of the maximum (device shows the most accurate value).

RESULTS

Table 2. *Organoleptic properties of the samples 24h, 15 days and 30 days after the preparation*

Formulation	Organoleptic properties
A_1	Clear, homogeneous, transparent gel, with a specific smell, easy to spread, the film after application on skin is thin, not sticky and greasy, and cause a pleasant feeling on skin, gel has a semi-solid consistency, can rinse with water, gel has small air bubbles.
A_2	Clear, homogeneous, transparent gel, with a specific smell, easy to spread, the film after application on skin is thin, not sticky and greasy, and cause a pleasant feeling on skin, gel has a semi-solid consistency, can rinse with water, with no air bubbles.
A_3	Crystal clear, homogeneous, transparent gel, with a specific smell, easy to spread, the film after application on skin is thin, not sticky and greasy, and cause a pleasant feeling on skin, gel has small air bubbles.

The results of measurements of pH values are given in Tables 3-5.

Table 3. *Results of measurements of pH values 24h after preparation*

Formulation	A_1	A_2	A_3
pH	5,11	5,13	5,12

Table 4. *Results of measurements of pH values 15 days after preparation*

Formulation	pH value			Average
	I measurement	II measurement	III measurement	
A_1	5,12	5,11	5,13	5,12
A_2	4,70	4,69	4,68	4,69
A_3	5,15	5,27	5,27	5,23

Table 5. *Results of measurements of pH values 30 days after preparation*

Formulation	pH value			Average
	I measurement	II measurement	III measurement	
A_1	5,14	5,15	5,10	5,13
A_2	4,68	4,63	4,71	4,673
A_3	5,26	5,27	5,22	5,25

Changes in viscosity of formulations A_1, A_2 and A_3, depending on the number of revolutions per minute, are shown in Figure 4-6.

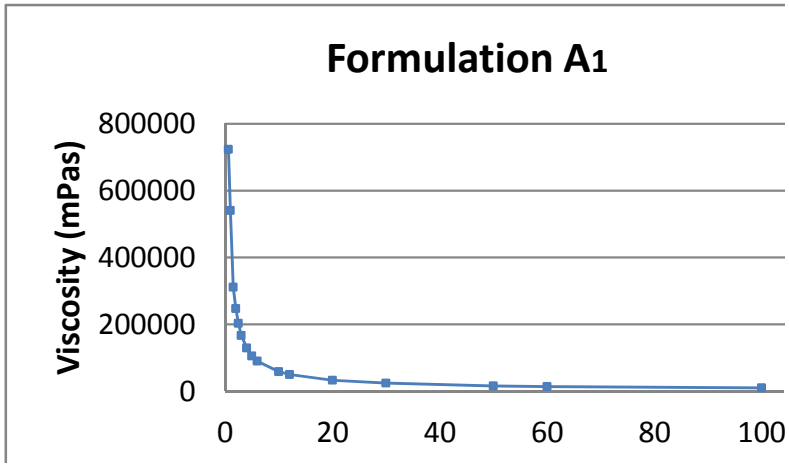

Figure 4. *Changes in viscosity of formulation A_1 depending on the number of revolutions per minute*

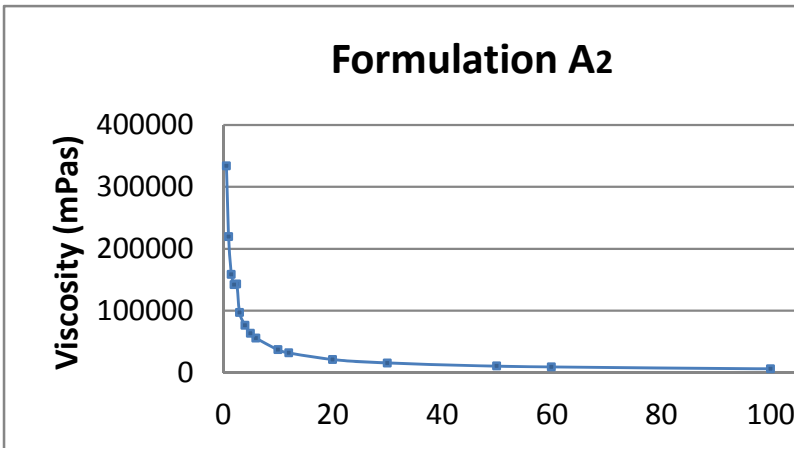

Figure 5. *Changes in viscosity of formulation A_2 depending on the number of revolutions per minute*

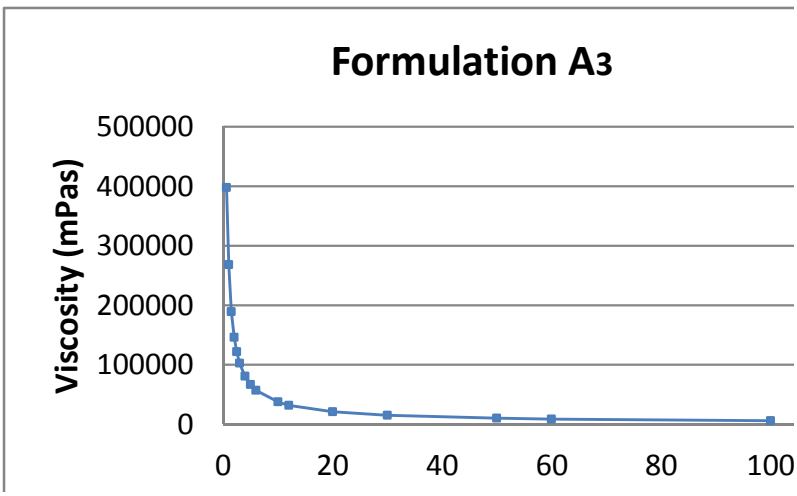

Figure 6. *Changes in viscosity of formulation A_3 depending on the number of revolutions per minute*

DISCUSSION

All formulations show similar organoleptic properties during the observed period of time and meet the criteria required for a certain type of products (in this case for vaginal gels). Gel with Carbopol® Ultrez polymer is distinguished by its homogeneity, easier and faster production and the absence of air bubbles that can be incorporated during mixing.

Measured pH values of the samples do not differ significantly compared to the normal pH of vaginal fluid (3.8 to 4.2) - pH values are within physiological values for the required application site. The results show that containers have no significant impact on the pH values of the samples.

The viscosity of the samples decreases with increasing the number of revolutions per minute (rotational speed). As the rotational speed is proportional to shear rate, increasing the number of revolutions, also increase the shear rate, but viscosity decreases.

By comparing the values of viscosity at 4 rpm (45.7%), we can conclude that a maximum value of viscosity has the formulation with Carbopol® 940 polymer, and the lowest value formulation with Carbopol® Ultrez polymer (A_2 formulation, which is identical to the formulation for the vaginal gel carrier in *Metronidazoli mucilago vaginalis 0.75%* - MF2008). Also, according to the results, we can see that the formulation of vaginal gel carrier which has the largest value of viscosity at the beginning of measuring, also has the largest value of viscosity at the end (sample with Carbopol® 940 polymer).

CONCLUSION

In this study we suggested the development of formulations for vaginal gel carriers in the pharmacy.

The conclusion is that vaginal gel carriers whose properties meet the requirements of the European Pharmacopoeia can be prepared in the pharmacy as magistral medicines. Optimal value for viscosity has a formulation A_1 (formulation with Carbopol® 940), so that the formulation is our recommendation for the development of vaginal gel carrier.

Because of the complicated procedure for registration of the generic drug (11, 12), recommended formulation for vaginal gel carrier, as magistral medicine, has a great importance for patients who require precise adjustment of therapy.

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RAZVOJ FORMULACIJA NOSAČA ZA VAGINALNE GELOVE U USLOVIMA APOTEKE - ASPEKT KVALITETA I REGULATIVE

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Sažetak

Na osnovu *Zakona o lekovima i medicinskim sredstvima* koji je na snazi u našoj zemlji, magistralni lek je lek izrađen u apoteci na osnovu recepta (formule) za određenog bolesnika - korisnika. U praksi se sve više javlja potreba za *ex tempore* izradom vaginalnih preparata u uslovima apoteka i galenskih laboratorija. Usled malog broja registrovanih preparata, tipa vaginalnih gelova, na svetskom tržištu, ali manje na našem, veoma je važna njihova magistralna izrada u uslovima apoteke.

Cilj ovog rada bio je ispitivanje mogućnosti izrade nosača za vaginalne gelove sa različitim hidrofilnim gelirajućim sredstvima u uslovima apoteke u skladu sa zahtevima Evropske farmakopeje. Za njihovu izradu korišćena su sledeća gelirajuća sredstva: Carbopol® 940, Carbopol® Ultrez 10 i Pemulen® TR 1 NF.

Sve tri formulacije pokazuju slična organoleptička svojstva u posmatranom vremenskom periodu. Izmerene pH vrednosti formulacija nosača ne odstupaju značajno u odnosu na normalnu pH vrednost vaginalne tečnosti. Najoptimalniji viskozitet ima formulacija A_1 (sa Carbopolom® 940), koja je ujedno i naša preporuka za nosač u izradi vaginalnih gelova. S obzirom na komplikovan postupak registracije generičkog leka, predložena formulacija nosača za vaginalne gelove, kao magistralnog leka, od velikog je značaja za primenu kod bolesnika kojima je neophodno precizno podešavanje terapije.

Ključne reči: **magistralni lek; nosač; vaginalni hidrogel; regulativa; viskozitet**