ISSN 1070-4272, Russian Journal of Applied Chemistry, 2009, Vol. 82, No. 8, pp. 1488−1493. © Pleiades Publishing, Ltd., 2009.
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MACROMOLECULAR COMPOUNDS AND POLYMERIC MATERIALS

Optimization of Rheological Properties of an Adsorption Vaginal Gel Based on Carbopol

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Received December 11, 2008

Abstract—Rheological properties of adsorption vaginal gels based on Carbopol were examined and compared with those of Metrogyl (USA). The formulation was optimized by the method of dynamic rheology, and the rheological extrusion optimum of the vaginal preparation was determined. The activation parameters of the formulations were calculated.

DOI: 10.1134/S107042720908031X

Aqueous polymeric gels are widely used in production of cosmetics and pharmaceuticals for improvement of their rheological characteristics [1–3]. The possibility of formation of a network structure in microgels is widely used in various applied programs, in particular, in production of soft medicinal forms (SMFs).

In the world's pharmaceutical practice, the most widely used materials for SMF base are synthetic high-molecular-weight acrylic acid polymers cross-linked with sucrose allyl ether or with pentaerythritol. In the leading pharmacopoeias, these materials are termed carbomers. The structural formula of carbomers consists of the following monomeric units [4]:

$$\left[-CH_3-\underset{\substack{|\\ COOH}}{CH}- \right]_n$$

Carbomers are finely dispersed white powders consisting of 2–7-μm particles. They can be readily dispersed in water with the formation of acidic colloidal solutions having low structural viscosity. After neutralization, these solutions transform into gels with a high structural viscosity [5]. Carbomers were chosen as a base for an adsorption vaginal gel because of the following advantages: (1) high viscosity at low concentration, (2) compatibility with many active components, (3) good bioadhesive properties, (4) temperature stability, and (5) excellent organoleptic characteristics and good tolerability by patients [6, 7].

One of the best known carbomer-based soft medinicals (SMs) for treating bacterial vaginosis is a hydrophilic gel produced in the United States under the name Metrogyl. It exhibits an antianaerobic effect. A distinctive feature of the developed SM is adsorption character of its effect on the affected area. In bacterial vaginosis (BV), the affections are local. Hence, the optimal solution is local treatment, in particular, sorption therapy. Adsorption vaginal gels are a new generation of SMs.

Because the rheological parameters directly affect the therapeutic activity of drugs (release, absorbability, duration of effect, etc.), their optimization and standardization is a major technological problem. Problems of scientific substantiation of SMF formulas are covered in the literature insufficiently, and therefore they are also of interest.

To ensure good therapeutic effect, it is necessary to provide proper characteristics of drug formulations, so as to ensure easy application of the gel and its prolonged contact with the mucous membrane.

In this study we examined the rheological properties of an adsorption vaginal gel developed on the basis of a carbomer. The acting substance is Enterosgel (EG) sorbent. In the development of an adsorption gel, it was necessary to find the optimal combination of the concentrations of the acting substance and structuring components.

The rheological method allows determination of the SM plasticity range and optimization of the combination of component concentrations for the required temperature conditions of SM storage and application.

For correct determination of rheological parameters, the viscosity characteristics of SMFs were studied not only at high loads (requirements of the technological "rheological extrusion optimum") but also at very low deformation rates corresponding to characteristics of manual gel application.

The investigation objects were as follows: Metrogyl soft medicinal (Metronidazole, US Pharmacopoeia) produced by Unique Pharmaceutical Laboratories, registry no. 011666/04 of June 28, 2004; Carbopol Ultrez (Carpbopolum, -934, -941, -940), a thinly cross-linked copolymer of acrylic acid and polyfunctional cross-linking agents (B.F. Goodrich Chemical); Enterosgel [FS (Pharmacopoeia Item) 42-3603-98] a methylsilicic acid hydogel, a white mass consisting of gelatinous lumps of various sizes, odorless and tasteless, virtually insoluble in water and 95% alcohol.

The medicinal for BV treatment was prepared by mixing as follows.

(a) Base gel. A calculated amount of purified water was placed in a mortar, and a calculated amount of gel-forming agent Carbopol was added with continuous stirring until it completely dissolved. Then the required amount of a 10 wt % KOH solution (fourfold amount relative to the Carbopol weight) was added to the mortar. The mixture was stirred until a uniform transparent gel formed.

(b) Adsorption gel. In the next step, to the ready base gel we added Enterosgel adsorbent in the required amount (10, 15, or 20% relative to the total weight).

The properties of the formulations were optimized by dynamic rheology with a modified Rheotest 2.1 rheoviscometer (Germany) equipped with a cylinder–cylinder measuring unit (ratio of radii 1.02) in the mode of controlled shear rate. The shear rate was varied in the range 0.1–800 s^{-1}, and the temperature, in the range 15–50°C. The measurement error was 3%.

The measurements showed that the hydrophilic base gel containing 0.1 wt % Carbopol Ultrez gel-forming agent (hereinafter, Carbopol) is a non-Newtonian fluid whose viscosity decreases throughout the examined range of shear rates, 0.1–800 s^{-1} (Fig. 1a). An increase in the mechanical load causes breakdown of structural associates. The viscosity decrease gradient at low shear rates is larger than at higher shear rates. This difference in the flow at low and high deformation rates for the formulations in hand is preserved at higher content of Carbopol in the hydrogels, which is characteristic of systems with weak intermolecular interaction. Supramolecular associates are capable of breakdown at relatively low shear rates (D = 0.1–1.0 s^{-1}). Carbopol

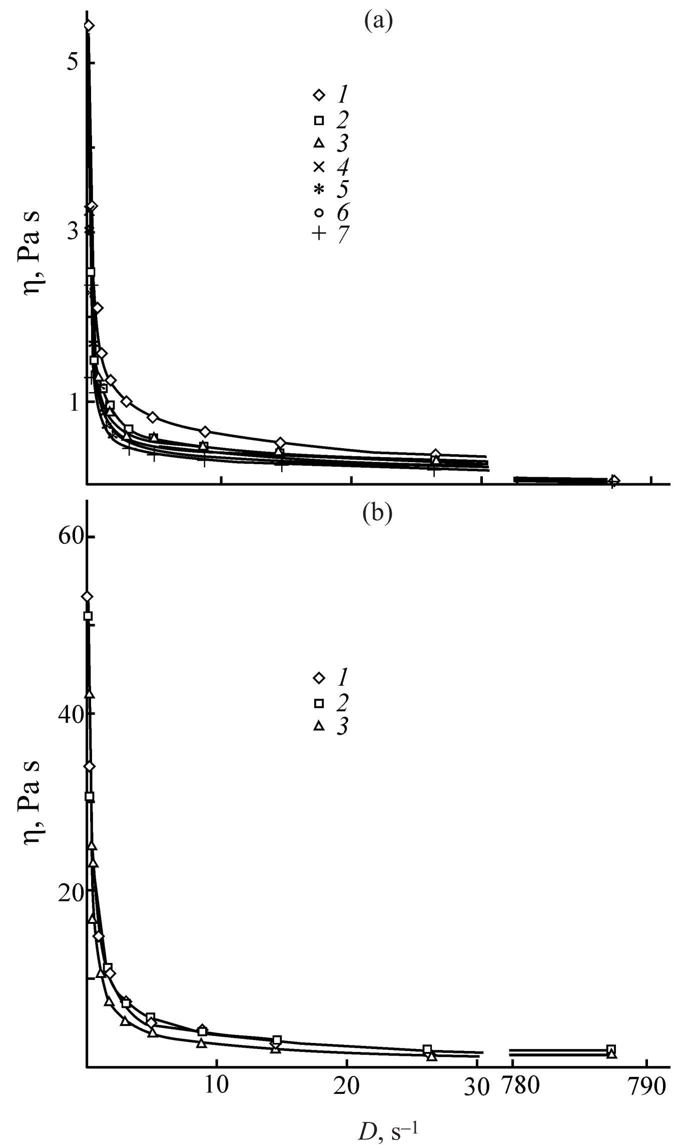

Fig. 1. Viscosity η of base gel containing (a) 0.1 and (b) 0.3% Carbopol as a function of the shear rate D at various temperatures. T, °C: (a) (*1*) 15, (*2*) 20, (*3*) 25, (*4*) 30, (*5*) 37, (*6*) 40, and (*7*) 50; (b) (*1*) 15, (*2*) 20, and (*3*) 50.

Activation parameters of Carbopol base gel and Carbopol + EG formulations at D = 25 s^{-1}

T, K	[Carbopol], 0.3%	[Carbopol], 0.3%+ EG], 10%	[Carbopol], 0.3%+ EG], 15%	[Carbopol], 0.3%+ EG], 20%
	ΔG_v, kJ mol^{-1}			
288	1.703	2.572	2.089	1.848
293	1.655	2.276	2.112	2.046
298	1.535	2.067	2.168	2.081
303	1.382	1.400	2.224	1.838
310	1.258	1.865	2.165	1.800
313	1.187	1.310	1.102	1.818
323	0.952	1.532	0.593	1.203
	ΔH_v, kJ mol^{-1}			
288–323	8.088	11.689	13.732	7.103
	$T\,\Delta S_v$, kJ mol^{-1}			
288	6.385	9.118	11.644	288
293	6.433	9.413	11.620	293
298	6.553	9.622	11.564	298
303	6.706	10.289	11.508	303
310	6.830	9.824	11.568	310
313	6.901	10.379	12.630	313
323	7.136	10.157	13.139	323
	ΔS_v, kJ mol^{-1} K^{-1}			
288–323	0.022	0.032	0.039	0.017

is a strong gel-forming agent. With an increase in its concentration in the base gel from 0.1 to 0.3 wt %, the viscosity of the systems increases by approximately an order of magnitude (Fig. 1b).

Pertsev et al. [7] experimentally evaluated the range of principal rheological characteristics (“rheological optima of consistency and coatability”) of hydrophilic and lipophilic SMFs, determining their optimal consistency from consumer’s viewpoint. To evaluate SMF consistency, they plotted the rheograms of its fluidity in the shear rate interval 1.5–1312 s^{-1} at 20°C (assumed temperature of ointment storage). The rheological consistency optimum in this interval of shear rates is characterized by the yield point of 45–60 Pa and effective viscosity of 0.34–108 Pa s. Pertsev et al. [7] believe that the rheological optimum of coatability of hydrophilic formulations on skin is satisfactory if the shear stress corresponding to a shear rate of 125–275 s^{-1} is 87–250 Pa. These parameters reflect the capability of a formulation for tube filling in packaging, its extrudability from tubes, and other technological properties of SM.

Using the procedure applied in [7] to determining the rheological extrusion optimum, we found the optimal concentration of Carbopol gel-forming agent. The extrusion optimum is exhibited by the base gel containing 0.3–0.5 wt % Carbopol. Taking into account specific features of application of this formulation as vaginal gel with Enterosgel sorbent which increases the viscosity, for further studies we chose the formulation with 0.3 wt % Carbopol.

Introduction into 0.3 wt % base gel of 10–20 wt % Enterosgel adsorbent increases the viscosity of the system by approximately 10–15%, i.e., formulations with EG exhibit still more pronounced non-Newtonian

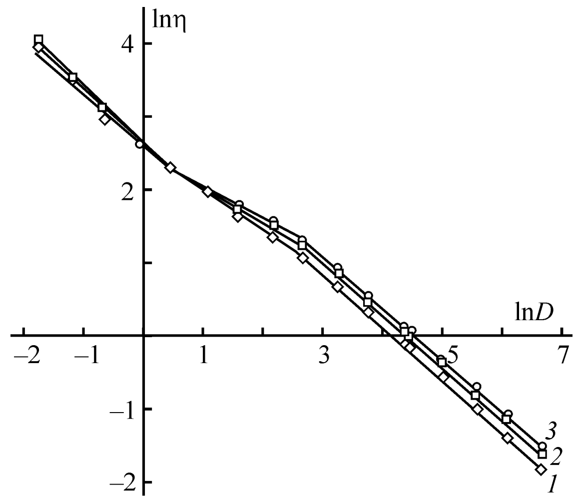

Fig. 2. Logarithm of viscosity ln η as a function of logarithm of shear rate ln *D* at various temperatures for samples containing (*1*) 0.3% Carbopol + 10% EG, (*2*) 0.3% Carbopol + 15% EG, and (*3*) 0.3% Carbopol + 20% EG.

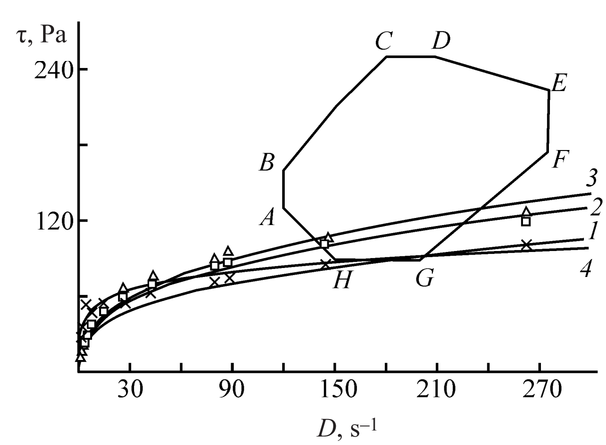

Fig. 3. Rheological extrusion optimum for various samples. (τ) Shear stress and (*D*) shear rate. (*1*) 0.3% Carbopol + 10% EG, (*2*) 0.3% Carbopol + 15% EG, (*3*) 0.3% Carbopol + 20% EG, and (*4*) Metrogyl. (ABCDEFGH) Boundary of technological extrusion optimum.

flow behavior (Bingham plastics, pseudoplastic fluids) [8, 9].

The shear rate–viscosity diagrams plotted in log–log coordinates for the base gel with 0.3 wt % Carbopol show no inflections, which suggests the absence of structural constituent in the sample. Similar dependence obtained at low shear rates for the formulations with Enterosgel revealed in the flow curves the regions determined by the contribution of the structuring agent to the viscous flow. In the formulations under consideration, EG, being an adsorbent and an active component, also behaves as a structuring agent (Fig. 2).

The presence of the yield point for all the formulations [the trend lines intercept nonzero portions on the shear stress (τ) axis] allowed them to be classed with Bingham plastics (Fig. 3).

For vaginal medicinal forms, the presence of a definite yield point is the required structural-mechanical parameter.

Because vaginal gels are applied, as a rule, at 37–40°C, the formulations used should have structural-mechanical properties ensuring the required viscosity and fixation ability for efficient interaction of the drug with the mucous membrane. At application temperatures of 37–40°C, the medicinal form should exhibit the required absorption and prolonged effect.

It was demonstrated previously by the example of liquid-phase materials for entomological purpose that the required key parameter, yield point, at which the formulation is held on a surface, for a vertical support 10^{-3} m thick is 9 Pa [10].

The yield point of the base gel, 0.3 wt % Carbopol Ultrez, in the temperature range 15–50°C is 9–10 Pa. Introduction of EG into the formulation in an amount of 10–20 wt % allows the yield point to be maintained on a level of 10–12 Pa at application temperatures, 37–40°C. Minor increase in the yield point of the formulation on adding EG is favorable for enhancing the sorption ability of the gel owing to an increase in the time of the drug action.

The optimal composition of the adsorption vaginal gel was determined taking into account the requirements of the rheological extrusion optimum, which was compared with that of the best of the available medicinals for this purpose, Metrogyl (USA).

Comparison of the rheological characteristics of the developed vaginal gels with different EG content and of Metrogyl shows that the rheological characteristics (viscosity, yield point) of the samples under consideration and Metrogyl are close. Addition of more than 20 wt % Enterosgel to the base gel leads to a considerable increase in the viscosity, which is not appropriate because of not only technological reasons (problems with packaging into tubes), but also inconvenience in use (problems with dosing and introduction with a syringe). The optimal rheological characteristics are exhibited by the formulations 0.3% Carbopol + 15% EG and 0.3% Carbopol + 20% EG. These formulations, like Metrogyl,

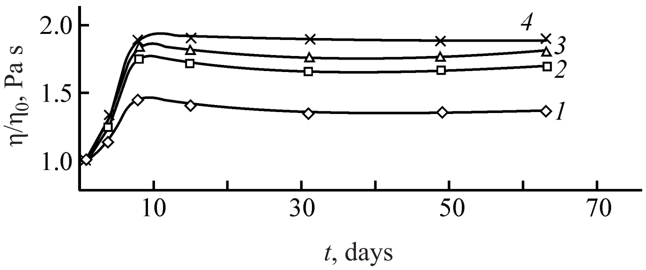

Fig. 4. Variation of the dynamic viscosity η/η_0 in the course of storage of a 0.3% Carbopol + 15% EG formulation at various shear rates (D = 0.5–87 s^{-1}). (t) Storage time.

are in the rheological extrusion optimum (Fig. 3). Formulations with a higher EG content are too viscous and have too dense consistency, which complicates accurate dosage and application of the gel onto the affected area of the mucous membrane.

On the basis of rheological data, we calculated for the formulations in hand the entihalpy ΔH_v, entropy ΔS_v, and Gibbs energy ΔG_v of activation of viscous flow [11].

The calculated values of free energy ΔG_v and entropy ΔS_v of activation of flow furnish additional information on the structure of the systems. The quantities given in the table were calculated for the shear rate D = 25 s^{-1} at which the formulations were subjected to mechanical actions and were partially broken down. The quantities ΔG_v and ΔH_v are positive in the entire composition range, because a flow is accompanied simultaneously by structure break and orientation of separate fragments. Both these processes require energy consumption; therefore, ΔH_v is positive. Positive values of ΔG_v and low values of ΔH_v suggest the presence in the formulations of supramolecular structures with weak intermolecular interactions. For a viscous flow of gels, the effect of the compensation of ΔH_v and ΔS_v is observed; therefore, ΔG_v is relatively low.

The activation entropy reflects complex processes of structure break accompanied by orientation of separate gel fragments under the action of deforming stresses. High shear stresses lead to cardinal changes in the initial structure of the formulation. To each stress corresponds a definite initial structure of the gel, and the elementary event in flow consists in a jump of separate segments from this new initial state into the activated state. Under the action of shear stress, the gel structure is broken, which is confirmed by a decrease in the activation entropy ΔS_v with an increase in the shear stress.

To evaluate the stability of the viscosity characteristics of the developed adsorption vaginal gels, we examined the behavior of the 0.3% Carbopol + 15% EG formulation in storage (Fig. 4). The measurements demonstrated good stability of the rheological parameters in storage. The laboratory sample was stored at 20°C in air with the aim to determine the shelf life and the life after unsealing. The sample is readily applied and preserved homogeneity. Therefore, it can be assumed that the vaginal gel developed can preserve viscosity characteristics for two and more months after unsealing, under definite storage conditions.

CONCLUSIONS

(1) The examined formulations are structured liquids with pronounced non-Newtonian flow behavior. They can be classed with Bingham plastics.

(2) The presence of 0.3 wt % Carbopol in the base gel ensures the required levels of viscosity, yield point, plasticity, and sorption characteristics of the formulations.

(3) The formulations have the yield point required of vaginal gels (10–12 Pa), which provides easy application onto mucous membrane and prolonged sorption in intravaginal application.

(4) The technological rheological extrusion optimum for the gel is attained for the formulations 0.3% Carbopol + 15% Enterosgel and 0.3% Carbopol + 20% Enterosgel.

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