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Thermoresponsive Hydrogels with Ultrasound-Controlled Properties

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Abstract—Possibility of creation of materials with transport properties operated by ultrasound on the basis of thermosensitive hydrogels modified by a solid phase of inorganic compounds is shown. The kinetic model of drug release from the hydrogel matrix, which allows to optimize the parameters of ultrasound exposure is proposed. Various options of devices with operated ultrasound an outlet of medicinal substance are offered.

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Development of materials with remotely controlled properties requires solving a range of problems associated both with synthesis of the material and selection of the optimal stimulus. There exists an especially urgent need for such materials in medicine, where their application would significantly enhance the possibilities for noninvasive therapy in treatment of a number of diseases, including malignant tumors. To this end it is necessary to develop a medicinal form capable, under external physical stimulus, of releasing the active substance into the region affected or to stimulate immediate destruction of the latter. Materials with remotely controlled properties can be conditionally called trigger, or "smart," materials.

The main criterion to be satisfied by materials with controlled properties is the ability to have their functional properties rapidly, selectively, and significantly changed in a reversible manner under exposure to a stimulus. The latter, in turn, should not cause damage to the material, have low intensity, and be localizable within the desired area. With regard to medicinal applications, these criteria are satisfied by a combination of a thermoresponsive polymeric hydrogel (material) with ultrasound (stimulus).

The suitability of stimuli-responsive polymeric hydrogels for the above-mentioned applications is determined by a number of their properties. Glassy in the dry state, hydrogels undergo swelling in aqueous solutions to become water-rich elastic gels abundant in dissolved compounds. This property of hydrogels is useful for introduction of drugs therein. The hydrogel synthesis procedure allows direct immobilization of various biologically active ingredients (enzymes, enzyme inhibitors, cofactors, etc.) [1–7]. Polymeric hydrogels can change their structure in response to physicochemical conditions of the medium: ionic strength of solution, pH, electric field, temperature. Among these factors, temperature is the most susceptible to local external regulation and therefore was chosen by us as the control parameter.

Thermoresponsive hydrogels exhibit reversible volume changes as a result of a phase transition experienced by the polymer chains once a certain temperature is achieved. In our case, this is the temperature at which the gel decreases in volume, the lower critical solution temperature (LCST). Structural changes undergone by a thermoresponsive hydrogel above this temperature cause the release of the drug entrapped into the surrounding medium.

Low-power ultrasound offers a number of advantages for application as an external physical stimulus. These include the targeting (achieved by focusing in the desired area), high permeability, relative safety of action, and a well-developed technical basis for ultrasound generation. The predominant mechanisms of the primary interaction of ultrasonic field with the medium depend both on the acoustic field parameters and the physicochemical characteristics of the

absorbing area [8]. In our studies, controlled release of active ingredient from thermoresponsive hydrogel was achieved under the influence of the temperature factor due to the thermal effect of acoustic action. The ultrasound frequency was 1–3 MHz, and the intensity did not exceed 2 W cm^{-2}. These parameters provide for nondestructive effect of ultrasound on the gel system in the precavitation mode and ensure fairly deep penetration of ultrasound into the gel volume.

A drawback suffered by thermoresponsive hydrogel carriers is a low ultrasonic absorption coefficient, little different from that in water, which complicates the production of selective heating effects by ultrasound. A solution to this problem can be found in "solid-phase sonosensitization" [9–11], in which technique a local increase in sensitivity of a given area of the system to ultrasound is achieved via introducing special modifiers, local ultrasound absorbers. Suitable as such modifiers are polydisperse solid-phase inclusions with high (compared to the surrounding medium) ultrasonic absorption coefficients, in particular, inorganic compounds: hydroxyapatite, goethite, barium sulfate, calcium carbonate, etc. [12]. It is essential that the preset distribution of the modifier phase over the sample volume determines the direction of the hydrogel density change in the LCST transition under ultrasound exposure and the associated change in the direction of the solution flow inside the hydrogel. Depending on the task set, the effects achieved through interaction of ultrasound with the modified area may be either reversible or irreversible.

Thus, controlled release of active ingredient or modification of its activity can be achieved through the use of a thermoresponsive hydrogel as the ingredient carrier and ultrasound for its thermal effect. In this case, local heating of the gel sample leads to a decrease in its volume as a result of the LCST transition and, thereby, to release of the active ingredient from the sample into the surrounding medium.

The implementation of the above-described approach is possible in principle, as demonstrated below by the example of a system comprised of a thermoresponsive hydrogel [poly(*N,N*-diethylacrylamide)] as carrier and ferrocerone and ovomucoid as model drugs. The main stages of development of this system (after selecting the material and setting the ultrasound parameters) are as follows:

– establish the possibility of a reversible (without structural changes) LCST transition for [poly(*N,N*-diethylacrylamide) hydrogel when subjected to ultrasound treatment in the mode selected;

– design a model for processing the experimental data on the active ingredient (drug) release from the hydrogel matrix with a view to determining the kinetic constant of the LCST transition of the hydrogel; and

– improve the use of ultrasound for controlling the release of the active ingredient from the gel or the activity of the gel-immobilized target product (solid-phase sonosensitization).

Ultrasound-Induced Structural LCST Phase Transition in Poly(*N,N*-dirthylacrylamide) Hydrogel

Under the action of low-intensity (1 W cm^{-2}) therapeutic ultrasound with a frequency of 2.64 MHz poly (*N,N*-diethylacrylamide) hydrogel undergoes an LCST transition with its volume decreasing several times when the temperature of the aqueous medium reaches the corresponding transition temperature (31°C). In this case, ultrasound acts as a heating agent for the hydrogel whose ultrasonic absorption coefficient and heat capacity are virtually identical to those of water. The thermal transition of the gel, caused by aqueous medium heating, and the ultrasound-stimulated transition differ in the direction in which the gel density changes inside the gel sample. In the former case the gel sample density increases from periphery to center in accordance with the temperature gradient, and in the latter case the density changes uniformly over the sample volume. It was also shown that the diffusion coefficients of the drugs in the hydrogel and the activation energy of the LCST transition of the hydrogel are unaffected by repeated ultrasound-induced LCST transition of the hydrogel. Hence, ultrasound produces a nondestructive action on the gel (at least as regards the gel permeability and the transition kinetics), which allows reuse of the sample in experiments.

A Model of the LCST Transition Kinetics for Hydrogel

An Aggregation Model of the Hydrogel Collapse

We attempted building a fairly simple kinetic model for experimental data processing on ultrasound-induced release of the diffusant from the hydrogel matrix with a view to optimizing the ultrasound treatment parameters.

In gel shrinkage, the major factor preventing the polymer matrix units from approaching one another

and occupying a more thermodynamically favorable position to form a "hydrophobic core" are hydration shells of the chains and hydrogen bonds (inter- and intramolecular), whose overcoming requires an activation energy. The hydrogel shrinkage time as determined by the kinetic characteristics is of much interest in the context of hydrogel applications.

To describe the hydrogel collapse, we will take advantage of the kinetic scheme proposed and applied by Smoluchowski [13, 14] in suspension coagulation studies.

Let c_i be the number concentration of aggregates consisting of i polymer units (from here on, i-aggregates), each of which occupies a site corresponding to a dense phase. An infinite system ($1 \le i < \infty$) of kinetic equations describing the process kinetics appears as follows:

$$\frac{dc_1}{dt} = -kc_1 \sum_{j=1}^{\infty} c_j, \tag{1}$$

$$\frac{dc_i}{dt} = 0.5k \sum_{j=1}^{i-1} c_j c_{i-j} - kc_i \sum_{j=1}^{\infty} c_j,\ 2 \le i < \infty, \tag{2}$$

with the initial condition at time $t = 0$, $c_1 = c_0$, $c_i = 0$, and $2 \le i < \infty$ corresponding to the first (original) nondense phase. The initial concentration of the units of the original nondense phase is presumed known.

The right-hand side of Eq. (1) and the second term on the right-hand side of Eq. (2) describe the rate of disappearance of i-aggregates (i.e., their coalescence with other aggregates), and the first term on the right-hand side of Eq. (2), the rate of appearance of i-aggregates via pair interaction (coalescence) of smaller aggregates. The kinetic constant in Eq. (2) appears as $0.5k$, rather than k, because in the sum describing the source of i-aggregates the $c_j c_{i-j}$ combination occurs twice. It should also be noted that, for even i, the $c^2_{i/2}$ term in the sum considered occurs only once, so the contribution from equal aggregates to the rate of appearance of i-aggregates is underestimated twofold. However, this contribution is very small compared to other interactions considered here and therefore can be neglected, which allows the use of kinetic equations in form (1) and (2). It should be emphasized that, in the kinetic model considered here, only one kinetic parameter k is independent of the size of the interacting aggregates. Smoluchowski reduced the problem (1) and (2) to a single equation:

$$\frac{dC}{dt} = -0.5kC^2,$$

$$C = \sum_{j=1}^{\infty} c_j,\ t = 0,\ C = C_0,$$

and obtained the solution in the form:

$$C = \frac{C_0}{1 + 0.5kC_0 t}. \tag{3}$$

By substituting (3) in (1) and (2) it is possible to sequentially calculate the concentrations of all the aggregates. For example, the concentration of the polymer matrix units occurring in the original (nondense) phase can be determined as follows:

$$\frac{dc_1}{dt} = \frac{-kc_1 c_0}{1 + 0.5kC_0 t},\ t = 0,\ c_1 = c_0. \tag{4}$$

Equation (4) has the solution $c_1^* = (1 + kt)^{-2}$, where $c_1^* = c_1/c_0$ is the dimensionless concentration of the polymer matrix units in the original phase (this quantity can also be regarded as the fraction of the mass of the polymer matrix occurring in the original phase), and $0.5c_0 = K$, kinetic constant of the hydrogel collapse.

It should be noted that Smoluchowski estimated the kinetic constant k for aerosol coagulation using expression $k = (8/3)K_B T/\eta$, where K_B is Boltzmann constant, T, temperature, and η, viscosity of the medium. This expression was derived from the formula for the mobility of unbound particles as due to the action of Stokes viscous force solely. In our case, this estimation procedure is inapplicable because of a substantially lower mobility of the polymer chain units.

It is advisable to introduce, along with c_1^*, the mass fraction P of the polymer occurring in the second (dense) phase:

$$P = 1 - (1 + Kt)^{-2}. \tag{5}$$

Next, using Eq. (5) we will demonstrate how the constant K can be calculated on the basis of the experimental rates of ferrocerone release from hydrogel.

Let ρ_1 and ρ_2 be the densities, kg m^{-3}, of the hydrogel in the nondense and dense phases, respectively, and ρ_{p1} and ρ_{p2}, densities, kg m^{-3}, of the polymer matrix (with water excluded) in the nondense and dense phases, respectively.

We will represent the dimensionless mass of the hydrogel occurring in the first (nondense) phase,

containing 1 kg of the polymer, as $m_1 = \rho_1/\rho_{p1}$. After collapse, the gel will entirely transform into the second, dense phase, and its dimensionless mass m_2 will appear as $m_2 = \rho_2/\rho_p$. The difference between m_1 and m_2 will be equal to the mass of the water removed, $m_w = m_1 - m_2$. To determine the mass of the water removed via collapse of one hydrogel granule, m_w should be multiplied by the polymer mass per granule $M_p = (4/3)\pi\rho_{p1}R^3$ (R is the initial granule radius). Further, the result should be multiplied by the mass fraction of the polymer P, because by the time t only this part of the hydrogel will transform into the second phase. To obtain the final expression for the mass of the water removed we have to consider the following point: In the first t_0 seconds of all the experiments on release of the ingredient from the hydrogel particle the ingredient is washed out by diffusion, and no phase transition occurs; the onset of the ultrasound action or thermal effect (heating) corresponds to the moment t_0. Consequently, it is necessary to replace t in formula (5) by $(t - t_0)$. The final expression for mass m_w of the water released by the time t from the granule with radius R has the form:

$$m_w = (4/3)\pi R^3(1 - [1 + K(t - t_0)]^{-2})\rho_{p1}(\rho_1/\rho_{p1} - \rho_2/\rho_{p2}). \quad (6)$$

By calculating the thickness h of the spherical layer, containing the water mass m_w, as $h = m_w/(4\pi R^2\rho_w)$ and substituting formula (6) into the latter expression we will arrive at:

$$h = (\mu/3)(1 - [1 + K(t - t_0)]^{-2})R, \quad (7)$$

where $\mu = (\rho_{p1}/\rho_w)(\rho_1/\rho_{p1} - \rho_2/\rho_{p2})$.

The thickness h will be used in the subsequent calculation of the mass transfer of the active ingredient from the hydrogel.

Mass Transfer of the Ingredient from the Hydrogel Particle, with Gel Shrinkage (Collapse) Taken into Account

Next, we will consider the diffusion process in the time interval $0 < t < t_0$ before the collapse onset. In this case it is necessary to take into account the fact that the active ingredient at the gel particle sphere boundary is entrained by the surrounding stream, so the concentration of the ingredient c at the sphere boundary can be taken as zero, $c = 0$. At the initial moment $t = 0$ the unperturbed condition as expressed in terms of the total mass of the ingredient in the initial particle M_0 appears as $c_b = (3/4/\pi)M_0/R^3$. The diffusion coefficients of the ingredients in the gel are very small, and the concentration wave will not reach the center of the sphere within time t_0. This allows the sphere curvature to be neglected, and the flux and concentration profile of the ingredient to be calculated with the use of the exact self-similar solution on diffusion of the ingredient from unlimited fluid to the absorbing surface.

Let the starting point of the X-axis be on the sphere surface and this axis be directed toward the center of the sphere. This problem has the known solution [15]:

$$c = c_b\phi(\xi), \quad (8)$$

where

$$\xi = X/(2\sqrt{Dt})$$

is the self-similar variable; D, diffusion coefficient of the ingredient; and

$$\phi = (2/\sqrt{\pi})\int_0^{\xi}\exp(-\alpha^2)d\alpha$$

is an error function integral [16].

The flux density j of the ingredient toward the surface of the sphere appears as follows:

$$j = -D\partial c/\partial X = -(c_b/\sqrt{\pi})\sqrt{D/t}.$$

Hence, the dimensionless mass $\alpha_1 = M_{out1}/M_0$ of the ingredient released from the particle within time t ($t < t_0$) (before collapse) can be calculated as follows:

$$\alpha_1 = \left(\frac{4\pi R^2}{M_0}\right)\int_0^t j dt = \frac{6}{\sqrt{\pi}}\frac{\sqrt{Dt_0}}{R}\sqrt{\frac{t}{t_0}}. \quad (9)$$

The moment t_0 corresponds to the onset of the hydrogel collapse and its accompanying water outflow. In calculation of the dimensionless mass of the ingredient $\alpha_2 = M_{out2}/M_0$ released from the particle within the time t after collapse ($t > t_0$) we should take into account the fact that, in the collapse stage, the water stream from the hydrogel will be depleted in the ingredient being released (due to the preceding diffusion stage). Hence, it is necessary to calculate by expression (8) the content of the ingredient in the spherical layer with the thickness h [see Eq. (7)], since specifically this water mass will be removed by the time t ($t > t_0$) (after collapse):

$$\alpha_2 = 4\pi R^2\int_0^h c_b\phi(\xi)dX = 6\frac{\sqrt{Dt_0}}{R}\int_0^s \phi(\xi)d\xi,$$
$$s = \frac{h}{2\sqrt{Dt_0}}. \quad (10)$$

Rate constants of the LCST transition of the ferrocerone-containing poly(*N,N*-diethylacrylamide) hydrogel. Calculation by formula (16)

t_1, s	α_{t1}	$K \times 10^3$, s^{-1}
1900	0.810	1.437
2000	0.820	1.357
2300	0.875	1.406

Thus, the dimensionless mass of the ingredient released by the time t will appear as follows:

$$\alpha = \alpha_1 + \alpha_2 = \frac{6}{\sqrt{\pi}} \frac{\sqrt{Dt_0}}{R} \left(1 + \sqrt{\pi} \int_0^s \phi(\xi) d\xi \right). \quad (11)$$

Calculation of the integral on the right-hand side of formula (11) leads us to the following expression:

$$\alpha = \frac{6}{\sqrt{\pi}} \frac{\sqrt{Dt_0}}{R} \left[\sqrt{\pi} s \phi(s) + \exp(-s^2) \right]. \quad (12)$$

Using relations (7), (9), and (12) at given D and K values it is possible to plot the curve of release of the active ingredient from the hydrogel particle, with the hydrogel collapse taken into account.

Determination of the Kinetic Parameters of the Hydrogel Collapse Model

The model proposed by us includes two kinetic parameters: the molecular diffusion coefficient D, $cm^2\ s^{-1}$, of the ingredient in the hydrogel and the collapse constant K, s^{-1}. The diffusion coefficient can be determined in an independent experiment and also can be derived from the left-hand branch of the $\alpha(t)$ dependence at $t < t_0$ (*i*.e., before ultrasound is switched on or heat treatment is started).

It should be noted that, in this section of the curve, the dimensionless masses of the ingredient α and α_1 coincide. By substituting $t = t_0$ in Eq. (9) we obtain:

$$D = \frac{\pi}{36} \frac{\alpha_{t0}^2 R^2}{t_0}. \quad (13)$$

Here αt_0 is the dimensionless mass of the ingredient released at the time $t = t_0$.

Next, we will use expression (13) to estimate the diffusion coefficient D_f for ferrocerone in the ultrasound-induced ferrocerone release experiment (see below). Substituting $\alpha t_0 = 0.312$, $R = 0.5$ cm, and $t_0 = 10^3$ s in Eq. (13) we will arrive at:

$$D_f = 2.127 \times 10^{-6}\ cm^2/s. \quad (14)$$

The kinetic constant of gel collapse K can also be determined from the $\alpha(t)$ dependence with the use of the right-hand ($t > t_0$) branch of the kinetic release curve of the ingredient (ferrocerone). It should be noted that, as regards determining the constant K, the portions of the $\alpha(t)$ curve are unequal. Indeed, it follows from Eq. (7) that the spherical layer thickness h is close to zero for times t that are close to t_0 (for simplicity, we will call them small times) and tends to increase with increasing t. Thus, in the case of small times with their corresponding small thicknesses h the release of the ingredient in the first diffusion stage will result in depletion of deeper layers, and the mass α should be calculated by a fairy complex general expression (12). By contrast, for large times and the corresponding fairly large spherical layer thicknesses h the concentration perturbations associated with the diffusion stage will be localized inside this layer, and a very simple expression interrelating α, t, and K will be applicable. The ingredient mass released will be equal to the mass of the ingredient originally contained in the spherical layer considered, regardless of the mass ratio of the ingredient released in both stages of the process. Therefore, for large times we have $M_{out} = c_b m_w$, which equality, considering Eq. (6), appears as:

$$\alpha = 1 - \mu[1 + K(t - t_0)]^{-2}, \quad (15)$$

where $\mu = (\rho_{p1}/\rho_b)(\rho_1/\rho_{p1} - \rho_2/\rho_{p2})$.

Next, we will demonstrate by a specific example that, for large times t, the calculations by formulas (12) and (15) give identical results. From expression (15), the desired constant K can be easily determined as follows:

$$K = [(1 - \alpha_{t1})^{-1/2} - 1](t_1 - t_0)^{-1}. \quad (16)$$

Using formula (16), we calculated the hydrogel collapse constant K for three large times in the ultrasound-induced ferrocerone release experiment (see table).

The average hydrogel collapse constant K was estimated at $1.4 \times 10^{-3}\ s^{-1}$, with minor scatter of K values not exceeding 4%.

We will use this value to estimate the hydrogel collapse time t_{coll}. Taking $t_{coll} = (t - t_0) = 2/K$ and using formula (15) we will arrive at $\alpha \sim 0.9$, which means that, within this time, the hydrogel will collapse by 90%.

Calculation of the Curve of Ferrocerone Release from the Hydrogel

Using the determined values of the kinetic constants D and K we calculated the entire ferrocerone release curve. The actual experimental conditions were as follows: ultrasound switched on at $t_0 = 10^3$ s, initial radius of the hydrogel particle $R = 0.5$ cm, ferrocerone diffusion coefficient $D = 2.127 \times 10^{-6}$ cm^2 s^{-1}, kinetic constant of the hydrogel collapse $K = 1.4 \times 10^{-3}$ s^{-1}, $\mu = 1$ [see formula (7)]. The dimensionless mass α of the active ingredient released was calculated by formula (9) for times $t < t_0$. As to times $t > t_0$ (after collapse), we calculated the spherical layer thickness h by formula (7) and using Eq. (10) obtained $s = h/(2\sqrt{Dt_0})$, after which we estimated the desired quantity, α, by formula (12).

Figure 1 compares the experimentally determined rates of release of ferrocerone from the hydrogel with those calculated by the above-described procedure. It is seen that the experimental points are well matched by the theoretical curve. The largest deviations, 30%, are observed in the middle part of the time interval. Considering a complex shape of the curve and the conditional $\mu = 1$ value, the match should be regarded as satisfactory, whereby the adequacy of the proposed kinetic model of the hydrogel collapse is confirmed.

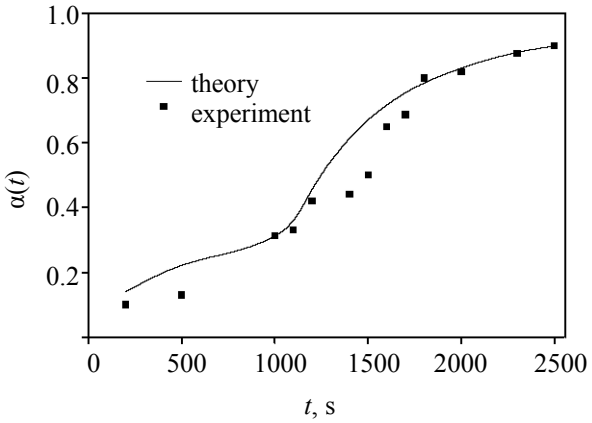

Fig. 1. Experimental data (points) and calculated kinetic curve of ultrasound-stimulated release of ferrocerone from the thermoresponsive poly(*N,N*-diethylacrylamide) hydrogel sample. Ordinate is the dimensionless mass α_t of the ingredient released.

Mass Exchange Between the Ingredient Granule and the Surrounding Hydrogel Shell

The application of ultrasound for controlling the drug release from the hydrogel is particularly efficient when the drug granule occurs at the hydrogel particle center. In this case, the temperature wave, along with the hydrogel contraction wave caused by ultrasound absorption and the corresponding heat evolution in the central granule, propagate from the center outward, so blockage of the aqueous drug solution by the dense hydrogel particles collapsed is avoided. In this context, mass exchange in different modes of ultrasound action is of interest. Here, we restrict ourselves to discussion of two cases of most considerable practical significance: single release of the ingredient from the hydrogel particle at a steady-state concentration distribution and release of the ingredient under periodic application of ultrasound.

Single Release of the Ingredient from the Hydrogel Particle at a Steady-State Concentration Distribution

For medicinal applications, the possibility of maximizing the amount of the drug released from hydrogel over a brief period is of interest.

In the single release case, the drug ingredient is released in the following regime. A hydrogel particle with a central drug granule occurs for prolonged time in a medium under conditions ensuring the removal of the ingredient from the outer surface of the particle (hydrodynamic flow, or a medium characterized by a much larger diffusion coefficient). In this case, a steady-state distribution of the ingredient concentration in the hydrogel particle volume will be established. The ingredient is released during the ultrasound-induced hydrogel collapse. Due to low diffusion coefficient of the ingredient in the hydrogel this regime can be maintained for prolonged time, thereby providing a broad selection of moments for switching on the ultrasound and ample possibilities for controlling the drug transport.

Under conditions where, on the surface of the drug ingredient granule with radius r_0, occurring at the center of the hydrogel particle with radius R, the equilibrium concentration c_s of the ingredient is maintained, and on the outer surface of the hydrogel particle ($r = R$, r is the current radius) $c = 0$, the distribution of the concentration c of the ingredient in the hydrogel is described by the equation:

$$c = \frac{r_0 c_s}{(R - r_0)} \left(-1 + \frac{R}{r} \right). \qquad (17)$$

The mass of the ingredient M_g contained in the hydrogel appears as:

$$M_g = \frac{2\pi}{3} c_s r_0^3(\gamma^2 + \gamma - 2). \quad (18)$$

Here $\gamma = R/r_0$ is the dimensionless radius of the hydrogel particle.

Sonication leads to collapse of the hydrogel particle, giving rise to release of the ingredient with the mass M_g from the hydrogel. Over the characteristic time of collapse $2/K$ (K is the kinetic constant of collapse), ~90% of the ingredient mass will be released. Thus, the average rate of release of the ingredient to the surrounding medium will be equal to:

$$v = 0.94 c_s K r_0^3(\gamma^2 + \gamma - 2). \quad (19)$$

It is seen that, as the dimensionless radius γ of the hydrogel particle exhibits almost quadratic growth, the rate of the ingredient release tends to increase. It will be of interest to compare this parameter with the ingredient flux under steady-state conditions $j = 4\pi D c_s r_0$:

$$v/j = 0.075 \mathrm{Pe_c}(\gamma^2 + \gamma - 2), \quad (20)$$

where $Pe_c = Kr_0^2/D$ is the modified Péclet number.

By substituting $K = 1.4 \times 10^{-3}$ s^{-1} and $D = 2.127 \times 10^{-6}$ cm^2 s^{-1} (yielded by processing the experimental data on ferrocerone release, see above), as well as $r_0 = 0.1$ cm and $\gamma = 10$, in Eq. (20) we will obtain $v/j = 53.2$.

Thus, the rate of release of the ingredient from the hydrogel particle that collapsed under the action of ultrasound exceeds more than 50-fold the steady-state diffusion flux of the ingredient through nondeformed hydrogel particle.

Release of the Ingredient from the Hydrogel Particle under Periodic Application of Ultrasound

Along with the single release regime in the ultrasound-enhanced drug transport, of substantial interest is the regime of periodic application of ultrasound and its action on release of the active ingredient from the polymeric hydrogel. In the periodic regime, a steady-state concentration distribution of the ingredient in the gel is not achieved. The optimal conditions of ultrasound exposure (periodicity) are determined by optimal combination of the following parameters: heating time to reach the LCST, gel collapse time, and gel cooling time. The heating time depends on the hydrogel properties (ultrasonic absorption coefficient) and the ultrasound parameters (frequency, intensity).

Here, we restrict ourselves to example of a model underlain by the two following presumptions.

(1) A sharp decrease in diffusion coefficient of the ingredient in the dense phase of the hydrogel (after collapse) allows neglecting the mass exchange via contact of the granule with the dense phase of the hydrogel. When ultrasound is switched off and the temperature drops below the LCST, the hydrogel captures water that does not contain the diffusant from the surrounding medium and transforms thereby into the nondense phase. This moment signifies the onset of the ingredient diffusion, which proceeds until ultrasound is switched on.

(2) The hydrogel particle is entirely collapsed. The residual concentration of the active ingredient in the dense phase is low, so after the hydrogel transformation into the nondense phase the hydrogel particle contains a liquid free from the ingredient transported.

Now we will consider the mass transfer rate for the ingredient under periodic application of ultrasound.

Let c_s be the saturated concentration of the ingredient in the hydrogel; D, diffusion coefficient of the ingredient; and r_0, solid granule radius.

According to [17], the mass of the ingredient M that passed from its granule to the hydrogel within time t_1 can be written as:

$$M = 4\pi r_0^2 c_s \left(\frac{Dt_1}{r_0} + \frac{2}{\sqrt{\pi}} \sqrt{Dt_1} \right). \quad (21)$$

The full time τ of periodic mass transfer of the ingredient can be represented as the sum $\tau = t_1 + t_2$, with t_2 incorporating the time of heating to reach LCST, the hydrogel collapse time, and the hydrogel cooling time.

The mass flux of the ingredient J, averaged over the period τ, is

$$J = M/\tau. \quad (22)$$

Under steady-state diffusion conditions the mass flux of the ingredient j to the nondense phase of the hydrogel is $j = 4\pi D r_0 c_s$, and it will be natural to introduce the $\beta = J/j$ factor indicating how many times the mass transfer increases due to periodic hydrogel collapse.

On rearrangements, we obtain from Eqs. (21) and (22) the following expression for the mass transfer acceleration factor:

$$\beta = 1 - \theta + \frac{2}{\sqrt{\pi}} \xi_d \sqrt{\theta - \theta^2}, \quad (23)$$

$$\theta = t_2/\tau;\ \xi_d = r_0/\sqrt{Dt_2}.$$

The β(θ) function has a maximum which is determined from the equation

$$\frac{d\beta}{d\theta} = -1 + \frac{\xi_d}{\sqrt{\pi}}(\theta - \theta^2)^{-0.5}(1 - 2\theta) = 0,$$

$$\theta_{max} = 0.5\left[1 - \sqrt{1 - \left(1 - \frac{\pi}{4}\xi_d^{-2}\right)^{-1}}\right]. \quad (24)$$

To get specific estimates, we will use the experimental diffusion coefficient for ferrocerone $D = 2.127 \times 10^{-6}$ cm^2 s^{-1}. With r_0 taken as 0.1 cm and t_2, as 1.5×10^3 s, we will arrive at $\xi_d = 1.77$, $\theta_{max} = 0.276$, and $\beta = 1.617$. It is seen that the application of ultrasound accelerates the mass transfer by 60%. However, for very large diffusant molecules, like, e.g., in the case of ovomucoid, the diffusion coefficient of the ingredient is by an order of magnitude smaller, and correspondingly the acceleration factor is significantly larger, $\beta = 3.70$.

From Eq. (23) it follows that the factor $\beta = J/j$ is unaffected by the hydrogel particle radius. Considering the fact that, with decreasing hydrogel layer thickness, the heating and cooling times tend to decrease, it can be concluded that, with decreasing hydrogel particle radius, the efficiency of periodically applied ultrasound will increase. The periodicity of ultrasound exposure at a given frequency is adjusted by selecting the intensity at which condition Eq. (24) is met.

Improving the Use of Ultrasound for Controlling the Release of the Active Ingredient from the Gel

Hydrogels containing more than 90% water exhibit low absorption of ultrasound. Therefore, the LCST transition of hydrogel under intense heat transfer conditions can require fairly significant ultrasound dosages. In some cases it is not possible at all to accomplish the structural phase transition with the use of low-intensity ultrasound. The ultrasound absorption can be enhanced by modifying the hydrogel with inorganic compounds. The modifier phase in the case of fairly large sizes acts as an internal heat source for a gel medium with a low absorption coefficient. Other conditions being equal, the ultrasound dosages required to achieve the desired temperature in the modified gel volume will be smaller compared to the unmodified gel (Fig. 2). It is essential that the unmodified hydrogel is heated virtually uniformly over the volume, and the heating rate of the modified gel with centrally localized inclusion is higher at the center than in the periphery of the sample. This fact

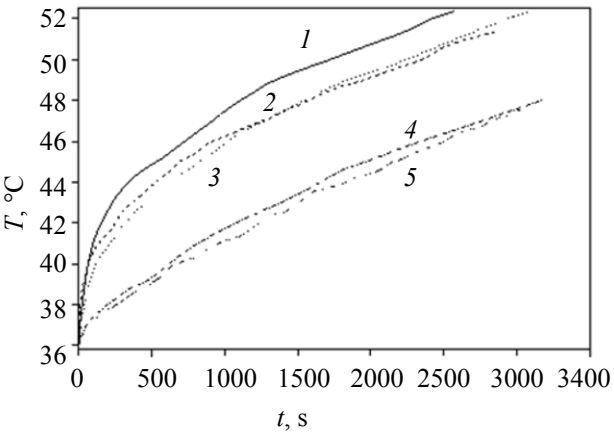

Fig. 2. Dynamic curves of ultrasound-induced heating of the gel sample (d = 1 cm) (*1, 2, 3*) modified with the centrally localized hydroxylapatite grain inclusion (m = 0.06 g) and (*4, 5*) unmodified. Measurement was made (*1, 4*) at the center of the sample, (*2*) at the 0.25-cm distance from the center of the sample, and (*3, 5*) at the 0.8-cm distance from the center of the sample.

determines the direction of change in the hydrogel density during structural rearrangement and the associated changes in the solution flows inside the gel sample.

In the case of the gel collapse in an ultrasonic field, hydroxyapatite inclusions localized at the center of the spherical samples determine the direction of increase in the gel density from center to periphery of the sample. When the sample is heated due to increase in temperature of the surrounding medium, the gel density changes in the opposite direction (from periphery to center). This difference is of much significance for cases where compounds with high molecular weights are transported from gels. Gel shrinkage due to heating, or to the action of ultrasonic field, causes arising of flows of the solution filling the gel matrix, that additionally contribute to the drug transport. In the case of thermally stimulated LCST transition of the gel these flows meet with a compacted layer formed in the periphery, spreading to the center of the sample, whereby the release of the solute is hindered because of difficulties in penetrating denser layers. For fairly large molecules, this may cause their complete blockage in the hydrogel matrix, like in the case of ovomucoid (M = 30000 amu).

When this process is initiated by ultrasonic field, the gel density tends to increase from center to periphery of the sample, which increase is particularly

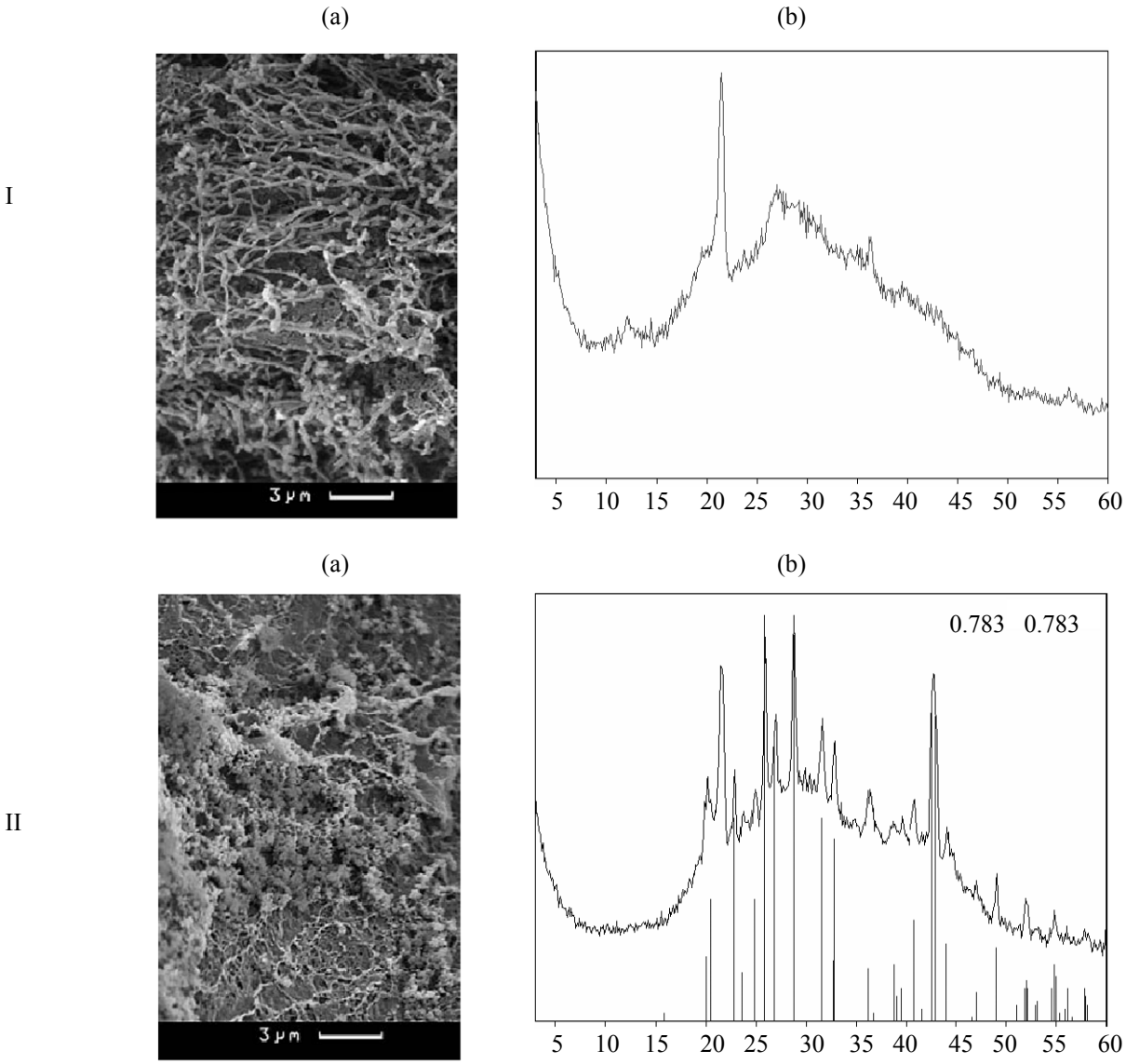

Fig. 3. (a) Electron micrographs and (b) X-ray diffraction patterns of an agarose hydrogel modified with (I) iron hydroxide and (II) barium sulfate.

sharp when the sound-absorbing inclusions are localized at the center of the sample. This motion promotes passing of the flows through the matrix under the precollapse conditions. The possibility for the solute molecules to be retained by the compacted gel network is lower, and ovomucoid is released from the gel. The rate of release exceeds by nearly two orders of magnitude the background release rate through the noncollapsed gel, which finding agrees fairly well with the calculated data. The sound-absorbing inclusion can simultaneously serve as a drug carrier, through interaction with the drug by adsorption or via its incorporation in the pore space. For example, introduction of hydroxyapatite into the gel causes the ferrocerone mass transported from the gel in the single release regime to decrease six times because of adsorption.

It should be noted that our preceding discussion concerned large localized inclusions. At the same time, the properties of hydrogels can be modified by highly-dispersed inclusions, if directed changes of the hydrogel density during structural rearrangement are not needed.

We synthesized samples, containing solid-phase sonosensitizers spread over the gel volume, by two

routes: by counter diffusion of reactants whose interaction results in formation of a poorly soluble compound in the preliminarily synthesized gel and by introduction of solid sonosensitizers in the course of the gel synthesis. These two routes may lead to different final structures of the sample, the major difference being that in the nature of bonding between the solid-phase sonosensitizer and the polymer matrix. In the former route, the polymeric matrix threads may participate in nucleation, growth, and aggregation of sonosensitizer crystals to which they get closely connected and whose shape and size distribution they determine. In the latter route this possibility is minimized, since the already formed crystals are introduced into the gel-like body being synthesized. Relevant literature [18] describes for the most part the second synthesis route, for which it is, however, difficult to estimate the contribution to ultrasonic absorption, made by the interaction of the solid phase with the matrix [19]. In our studies we used both routes but gave preference to the counter-diffusion route in situations when it was essential to assess the role of the solid phase–matrix interaction [20].

Experimental data are indicative of the presence of at least two types of localization of the solid phase crystallized in hydrogels. The probability of realization for each of these types depends on the nature of the solid-phase sonosensitizer and the polymer matrix. In the case of an agarose gel modified with iron hydroxide(III), the electron microphotograph (Fig. 3a) demonstrates a uniform distribution of the finely-dispersed modifier over the matrix threads, and no sites of preferential localization of the solid phase are seen. The diffraction pattern (Fig. 3b) also confirms the lack of iron hydroxide crystallites with notable sizes.

In the case of barium sulfate modifier, the electron microphotograph illustrates a qualitatively different pattern indicative of the presence of a dispersed crystalline phase localized on individual elements of the carrier matrix, as confirmed by X-ray analysis.

Earlier, we obtained similar results for iron(III) hydroxide and octa-4,5-carboxyphthalocyanine cobalt calcium salt modifiers deposited on a poly(*N,N*-diethylacrylamide) gel matrix [12]. The presence of two localization types for the modifier suggests that such systems may also significantly differ both in the acoustic effects and permeabilities.

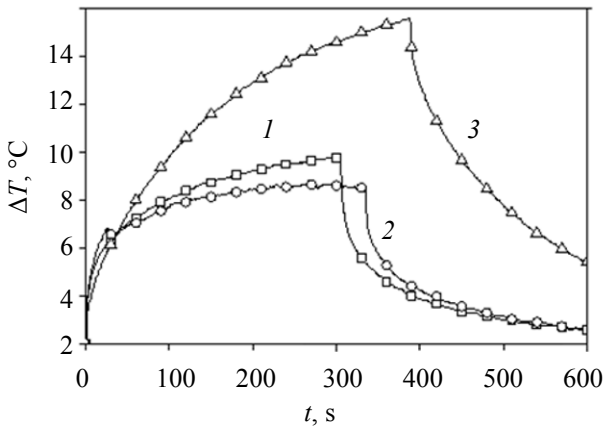

Fig. 4. Thermal effects from acoustic field exposure of an agarose hydrogel (3%) (*1*) unmodified and (*2, 3*) modified with (*2*) iron hydroxide and (*3*) barium sulfate (2 wt %). Ultrasound parameters: frequency 2.64 MHz, intensity 2 W cm^{-2}.

By way of example, Fig. 4 shows typical curves demonstrating the temperature rise behavior for the agarose hydrogel samples modified with iron hydroxide and barium sulfate when exposed to ultrasonic action. At identical solid phase concentrations the thermal effect for the barium sulfate-modified sample significantly exceeds that for the sample modified with iron hydroxide. A possible reason is the change in the mechanical characteristics of the matrix network which, in the case of iron hydroxide, is encrusted with the modifier, whereby the viscoelastic properties of the sample are affected.

At the same time, surface modification of hydrogel samples with iron hydroxide, by contrast to barium sulfate, causes the background (not associated with the action of ultrasound) rate of diffusion of selected drugs (furacilinum, ferrocerone) to decrease by nearly an order of magnitude due to formation of a dense blocking surface layer. This allows the use of iron hydroxide for synthesizing at the sample periphery of a "stopping layer" with a view to decreasing the background drug release. In this case, the direction of spread of the heat front in the sample will not be affected, because surface blocking by iron hydroxide does not cause the thermal effect from ultrasound action to increase. As seen from Fig. 5, the background release rate of ferrocerone from the gel modified at the periphery is smaller compared to the unmodified sample. The ferrocerone dosages released during the gel shrinkage cycle also decrease, giving rise to another possibility for controlling the transport parameters of the target ingredient.

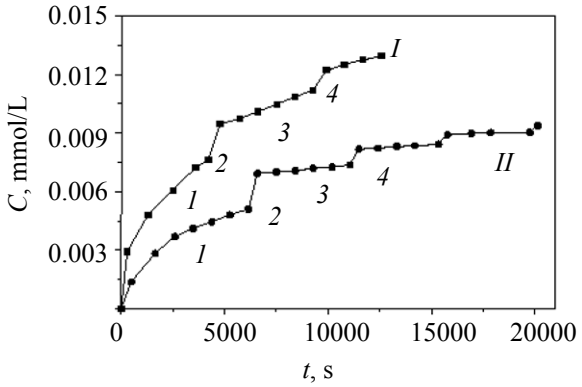

Fig. 5. Kinetic curves of release of ferrocerone entrapped in the gel in the solid state from the sample (*I*) unmodified and (*II*) modified with iron hydroxide along the periphery.

Thus, by optimizing the combination of several factors, namely, the hydrogel properties, the size and localization of inclusion, and the porosity and sorption capacity of the inclusion with respect to the drug substance, as well as the ultrasonic absorption coefficient and the sonication mode it is possible in principle to develop devices for ultrasound-controlled drug release [9, 21].

We developed techniques in which gel and polymer structures are used for synthesizing membranes whose permeability can both decrease and increase under the action of ultrasound, depending on the specific design of the device in which thermoresponsive hydrogel materials are used.

Introduction of a permeable porous substrate, exhibiting high ultrasonic absorption, causes the gel membrane permeability in an ultrasound field to decrease several times. For example, at the ultrasound frequency of 2.64 MHz and intensity of 1 W cm^{-2} the permeability of the poly(*N,N*-diethylacrylamide) membrane for antibiotic lincomycin decreases virtually by an order of magnitude. The reason is an increase in the gel density due to heating in the ultrasonic field of a porous substrate possessing high ultrasonic absorption properties. This also causes changes in the nature of the pore structure itself: The hydrophobicity increases as a result of the LCST transition of the gel. Enhanced hydrophobicity of the gel membrane also contributes to a decrease in permeability for hydrophilic compounds.

Figure 6a demonstrates the changes in the performance of the modified membrane whose permeability decreases under the action of ultrasound. Introduction of a distributed modifier provides for uniform contraction of the gel membrane.

The performance of another type of membranes, specifically those with permeability increasing under the action of ultrasound, is shown in Fig. 6b. A permeability increase is achieved via combining the stopping thermoresponsive gel plugs with materials having high ultrasonic absorption coefficients. Preferential heating of the material causes a decrease in the hydrogel plug volume mainly in the area contacting the framework material. This leads to a fault in the gel plug–framework contact and, depending on conditions, to an increase either in the fluid flow or in the diffusion coefficient of the target product.

The above-described approach to development of materials based on solid-phase-modified polymers with ultrasound-controlled transport properties is in the model development stage now. The greatest progress in implementation of this approach has been made in a relatively new field of cancer therapy, chemoembolization.

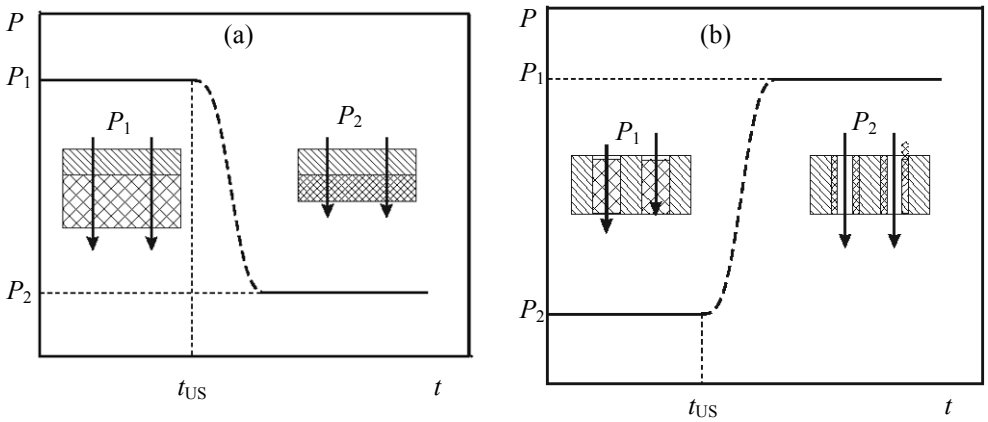

Fig. 6. Variation of the permeability p of the modified hydrogel membrane in an ultrasonic field: (a) decrease and (b) increase.

Chemoembolization (endovascular regional treatment) is a method used for local chemotherapy of malignant tumors of different localizations via luminal occlusion by an embolic material containing an anticancer drug, with artery blocked to stop the blood supply to the tumor. Microspheres get "stuck" in the microvasculature, thereby stopping the blood flow in the tumor, and start to release the cytostatic drug. For advantages offered by this method, see [22, 23].

Currently, microspheres are not produced in Russia; drugs are fairly expensive. In this situation, clinicians set themselves a task to develop a domestic analogue of microspheres for chemoembolization and improve the efficiency of regional endovascular treatment with the use of external physical stimuli. One of the possible options consists in application of porous hydroxyapatite microspheres encapsulated in a biocompatible thermoresponsive hydrogel as embolizing agent and of ultrasound as external stimulus. Due to biocompatibility of hydroxyapatite [24, 25] and a well-established technology of its synthesis it is possible to prepare samples with desired sizes and porosities [26].

The chemoembolization procedure suggested by us consists in the following. The vessel of the tumor is embolized by any known method (a "plug" is created). Next, a thermoresponsive hydrogel suspension containing a cytostatic and a finely-dispersed ultrasound absorber hydroxyapatite are introduced into the embolized vessel. Hydroxyapatite simultaneously acts as an additional source of the cytostatic immobilized therein. Under the action of ultrasound, as a result of a local temperature rise, the gel shrinks, and a certain portion of the cytostatic is released into the tumor. When ultrasound is switched off, the gel volume is restored, and the content of the cytostatic in the gel is replenished by desorption from the carrier (hydroxyapatite). The rate of inflow of the cytostatic into the tumor between the ultrasonic exposures is determined by its rates of is release from the carrier and of diffusion in the gel. The critical temperature of hydrogel (the contraction onset temperature) and the degree of contraction, determining the amount of the cytostatic released, can be adjusted by varying the chemical composition of the gel during synthesis.

Thus, the physicochemical approach to creation of materials under development is underlain by local conversion of acoustic to thermal energy on the solid-phase inclusions in polymer materials and may provide a basis for manufacture of devices for chemical and medicinal applications. Overcoming considerable obvious technical difficulties associated with implementation of this approach will take some efforts which, however, will be rewarded by equally obvious advantages.

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