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The Long-term Release of Antibiotics From Monolithic Nonporous Polymer Implants for Use as Tympanostomy Tubes*

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Abstract

A technology is elaborated for the fabrication of a novel tympanostomy tube (TT) from solidified polymer melts (Elvax and Polyurethane) and antibiotics (Ciprofloxacin and Usnic acid) for insertion into tympanic membrane (ear drum) according to the established surgical procedure. The long-term *in vitro* release kinetics of the antibiotics into liquid water has been assessed using standard methods. The measured kinetic curves revealed two stages of antibiotic release into the finite space. During the first stage (fast), the fast release rate is almost invariant and is determined by the diffusion through the steady diffusion layer formed due to solution agitation. In this first stage, the influence of the initial internal transport is weak because it takes place at negligibly small distance from interface and accordingly, at negligibly concentration drop. After the antibiotic concentration decreases within the much broader layer of matrix near interface, the internal transport becomes important. This manifests itself as the second stage in measured kinetics of release curves which is characterized by a gradual decrease in rate. The minimum inhibition concentrations of three antibiotics/antimicrobial compounds for four bacterial species were measured. The first stage of fast release from the polymer implant lasts 6 days at a polymer loading by Ciprofloxacin (0.03 g/cm³) and this was sufficient for preventing biofilm formation on the surface of the implant material. The measured kinetic curves of drug release showed more rapid decrease in the release rate compared to the Higuchi approximation. Comparison with existing theories, which account for the finite rate of drug dissolution, showed that this may explain the observed deviation from the diffusion-controlled Higuchi model. Large dimensions of drug particles and their aggregation retard the dissolution stage and consequently the release rate. Melt blending was found to cause the drug particle aggregation within polymer matrixes which was confirmed by microscopic reexamination of the polymer implant materials.

Keywords

Drug release; Extrusion; Drug particle aggregation; Drug dissolution rate; Drug particle size; Otitis media; Tympanostomy tube; Monolithic nonporous polymer implants

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1. Introduction

Antibiotic release from polymer implants is considered an important topic of “Formulation Science” [1], which, in turn, is an important novel branch of Surface and Colloid Science [1]. Different kinds of polymer systems are currently used in drug release, for example, reservoir and monolithic systems [2]. The monolithic systems are used for drug release from polymer implants and we shall pay attention to them. Monolithic systems are classified as either micro-porous or nonporous.

Micro-porous systems allow rapid release because the diffusivity of drug molecules in pores is rather high. However, such systems are not valid for long-term release because the entire drug content is released during rather short time, i.e., the release rate is high. Since the long-term release of drug is desirable for some applications, e.g. otitis media (OM) treatment, we restricted our attention to the nonporous monolithic polymer implant systems.

Monolithic dispersions can be prepared by producing polymer matrix in the presence of solid drug particles. The rate of drug transport within polymer matrix determines the rate and the duration of drug release from the implant. While there is a large specificity in mechanism of drug molecule diffusion, this predetermines the specificity in quantitative model of drug transport. In particular, the classical equation for non-steady diffusion [3] is not valid for them. If a drug is added in such a way that the drug concentration inside a polymer matrix is larger than the drug solubility, the device is called a monolithic dispersion. In this case, extra drug exists as particles in the polymer matrix as indicated by black dots in Fig. 1.

In diffusion-controlled dosage forms, drug molecules have to diffuse through polymer matrix to be released. Drug diffusion through polymer matrices depends on the size of drug molecules and space available polymer chains. Even though the space between polymer chains may be smaller than the size of drug molecules, drug can still diffuse through the polymer chains owing to the continuous movement of polymer chains by Brownian motion [2]. The local freedom of movement of the polymer chains may provide the local microscopic viscosity, which could be quite low. Thus, the local movement of the polymer chains is an important factor for determining the diffusion coefficient of drugs. Furthermore, if the solid drug is finely divided, uniformly suspended and rapidly dissolved, then a two-zone system will develop, as illustrated in Fig. 1. In the region closest to the receiving chamber [$0 < x < h(t)$], all of the solid will have dissolved and the drug will be present in concentration below the solubility limit, C_s . Further away from the receiving chamber, the drug will still be present as a solid suspension at the original starting concentration, C_0 .

About 50 years ago, Higuchi [4,5] assumed a linear concentration in the dissolved zone, as illustrated in Fig. 1, which is reasonable assumption when $C_0 \gg C_s$. He then required that the dissolution boundary $h(t)$ be located so that the mass of drug left the formulation is equal to the amount of drug which has diffused across the boundary at $x=0$ into the receptor chamber.

The polymer property, which is the most important for drug release is the solubility ratio [2]

$$R = C_s / C_0 \quad (1)$$

In Higuchi's development, the time required for all of the drug to dissolve t_f is given by

$$t_f = (1 - R/2)L^2 / 2RD \quad (2)$$

where D is the diffusivity of dissolved drug within polymer matrixes

As the total amount of drug $M_0 = LSC_0$ (S is the cross-section of diffusion stream), one obtains from Eq (2), the fraction of released drug

$$Q = \frac{M_R}{M_0} = \sqrt{\frac{2DtR(1 - R/2)}{L^2}} \quad (3)$$

The Higuchi approximation was developed assuming small R . The applicability boundary was determined later from exact solution [6]. Since this rigorous theory is rather complicated, approximate analytical solutions were proposed in [7]. A simple adjustment of the original Higuchi equation was proposed in [8]

$$Q = \sqrt{2[1 - R(\frac{\pi - 2}{\pi})]R\tau} \quad (4)$$

where $\tau = Dt/L^2$. It drastically reduced the deviation from exact solution in [6] for not small R . Although this is an improvement over Higuchi prediction, the error in Eq (4) is still rather large, nearly 30%, for $0.8 < R < 0.98$. For high R values, a representation more accurate than Eq (4) was derived in [9].

It is noteworthy that modeling the kinetics of drug release is essentially different for nonporous and porous diffusion-controlled polymer monolithic drug delivery systems [8]. Many measurements of drug release use an artificial membrane to physically separate the topical formulation from receptor liquid. An artificial membrane may contribute additional resistance to drug transfer into the receptor solution [10]. This may also occur in membrane absence as well due to the formation, within the solution, of the diffusion boundary layer [11,12] near the matrix surface. The solution stirring does not remove this boundary layer completely. The boundary diffusion layer is ignored in some models; this is known as “sink” boundary condition. Initially, the Higuchi approximation included the sink condition as well which was an essential limitation. Later, the Higuchi approximation was perfected by revising the sink boundary condition.

1.1. Kinetics of drug release from dispersion monolithic nonporous matrix with a boundary layer

The elimination of the sink condition from the Higuchi theory was made by Higuchi himself [13]. He clarified [13] that his approximation assumed “the rate limiting step was the diffusion of drug from the matrix (matrix controlled)”, while “the rate of diffusion from the surface of the matrix to the surrounding bulk solution will make a significant contribution to the total diffusion process” [13]. The notion of the diffusion layer thickness δ which accounts for possible spatial non-uniformity was ignored (Fig. 2).

This enables one, to describe the diffusion flux within the diffusion layer and at its boundary with matrix as

$$dM/dt = -D_a(C_a'(t) - C_b(t))/\delta \quad (5)$$

where D_a is the drug diffusivity in water, $C_a'(t)$ and C_b are the drug concentrations within boundary layer on its boundary with matrix and in the bulk of solution outside the diffusion layer and M is the amount of released drug normalized per unit area of S .

A similar expression of the Higuchi approximation is valid within quasi-steady diffusion layer of matrixes

$$dM/dt = -D(C_s - C_s'(t))/h(t) \quad (6)$$

The r.h.s. in Eqs (5) and (6) are equal that interconnects 3 unknown functions of time $C_s'(t)$, $C_a'(t)$ and $h(t)$.

The concentration at matrix/solution interface $C_s'(t)$ and $C_a'(t)$ are interconnected due to local quasi-equilibrium by the partition coefficient

$$K = C_s'(t)/C_a'(t) \quad (7)$$

Combining Eqs (5), (6) and (7) enables one to express $C_s'(t)$ and $C_a'(t)$ through $h(t)$. Taking this into account, dM/dt is expressed through $h(t)$. The Higuchi approximation for the equation of mass balance is transformed in a differential equation of first order for $h(t)$. Its simple integration yields an equation for $h(t)$, and accordingly for cumulative release $M(t)$ in the form of a square algebraic equation:

$$\left[\frac{M(t)}{(C_0 - C_s/2)} \right]^2 + p \left[\frac{M(t)}{(C_0 - C_s/2)} \right] - qt = 0 \quad (8)$$

Its solution is:

$$\left[\frac{M(t)}{(C_0 - C_s/2)} \right] = \frac{p}{2} \left[-1 + \sqrt{1 + \left(\frac{2}{p} \right)^2 qt} \right] \quad (9)$$

where

$$p = 2\delta DK/D_a; q = 2DC_s/(C_0 - C_s/2)$$

At sufficient long time

$$qt(2/p)^2 \gg 1 \quad (10)$$

$M(t)$ dependence reduces to the classical Higuchi equation (3).

At sufficient short time

$$qt(2/p)^2 \ll 1 \quad (11)$$

$M(t)$ dependence becomes linear

$$M(t) = (D_a C_s / K \delta) t \quad (12)$$

This corresponds to the initial almost uniform drug flux through the diffusion layer, when the solute concentration near polymer/water interface decreases only slightly due to high rate of internal diffusion, when the dissolved layer is yet thin. Later the gradient of solute concentration within matrixes decreases (because the distance $h(t)$ between solid/solution interface and solution/water interface increases), that corresponds to onset of Higuchi regime.

Two stage kinetics of release was confirmed [13] in experiments with Medroxyprogesterone Acetate. A similar modeling is described in [14].

The final equation of this theory is simple because it is derived with the assumption that the concentration in the solution bulk is zero which corresponds to infinite large volume of receiving chamber. This condition can be approximately satisfied when the volume of receiving chamber is sufficiently large. As the amount of drug is known, the maximal concentration in the receiving chamber, which is achieved at the end of the drug release, can be easily estimated as a function of the volume of receiving chamber. Nevertheless, the account for small drug concentration in bulk of solution becomes necessary, when the final stage of the release is of interest. This occurs because the concentration $C_a(t)$ becomes very low and comparable with $C_b(t)$, i.e., the diffusion flux in water, which is proportional to the difference $C_a(t) - C_b(t)$, is described with not small error. The theory of the diffusional release of a dispersed drug from planar and spherical matrixes into the finite external volume is proposed in [15]. Although the theory is analytical, its application is not easy because the final equation is very bulky. The theory for the same task was proposed in [16] which, however, was criticized [17].

1.2. Use of Tympanostomy Tubes for the Treatment of Otitis Media by means of its placement into tympanic membrane (ear drum) by surgery

Otitis media (OM) remains a serious public health problem and is a leading cause of hearing loss in the United States. Placement of tympanostomy tubes (TTs) can dramatically alter the course of recurrent and chronic otitis media, but in a significant percentage of patients, problems remain. Chronic post-tympanostomy tube otorrhea (P-TTO), recurrent acute otitis media with tympanostomy tubes, and early TT replacement are problematic with high healthcare costs and morbidity. P-TTO is especially problematic because it is often refractory to treatment and inflicts significant morbidity in the form of hearing loss and long-term middle ear dysfunction. Drs. Post and Ehrlich at the Center for Genomic Sciences (CGS) have uncovered evidence [18] and developed hypotheses that complex bacterial communities in the form of biofilm play a predominant role in otitis media. The next logical step is to develop methods that target the treatment of biofilm-mediated otologic disease. One method is to develop biofilm-resistant materials for use as an implant designed for use in the middle ear. The most common middle ear implant by far is the tympanostomy tube. Novaflux and CGS have discovered that polymeric implant materials made by incorporating special combinations of antimicrobial and antibiotic compounds are effective in inhibiting bacterial attachment and biofilm adhesion of the microorganisms associated with OM. The enabling feature of this novel technology platform stems from the ability to use traditional polymer-processing methods and equipment to readily design and make polymer blends with multiple antimicrobial active compounds. This approach would enable one to incorporate specific combinations of antimicrobial chemical entities directly in polymer implants and to capitalize on the vast advances being made in two highly-developed sciences of polymer blending and combination therapy of antimicrobials/antibiotics. These combinations would be impossible to make with the current coating technologies commonly used to make medical implants.

The first stage of developing is to determine and verify the release kinetics. This comprises the investigation of the drug release *in vitro*. We discovered that the measured kinetic curves of drug release is difficult to interpret using the Higuchi approximation, which is well recognized in many studies involving long release from monolithic nonporous matrix. This forced us to first consider the state of the drug release modeling in the case of monolithic nonporous delivery systems, and second to clarify how modeling is used in the interpretation of kinetic experiments. We found that the current level of modeling presents a large opportunity for experiment interpretation and that the utilization of those opportunities is often scarce. As the existing modeling became very helpful for interpretation of our experimental data, we believe that this experience may be useful and accordingly deserves publication. This is the objective of this paper as well as the characterization of the first stage in the elaboration of polymer drug delivery implant system such as a long-term antibiotic releasing tympanostomy tube.

2. Material and methods

2.1. Materials

a) Host Polymers—Two host polymers were used, as follows: 1). “Pellethane 2363-90AE” was used as our thermoplastic polyurethane elastomer (PU). This polymer has undergone biocompatibility testing in accordance with USP Class VI guidelines. The Shore A hardness of this polymer is 90A; it is a tough rubbery material based upon methylene diisocyanate (MDI), poly tetramethylene oxide, and 1,4 butanediol. [19,20]. 2). The ethylene-vinyl acetate copolymer used was “Elvax 560,” which contains 15% vinyl acetate (VAc). Hardness is 98 Shore A. It has a history of successful use as an implant material. [21].

b) Antimicrobials and Antibiotics—After considering a number of compounds with antimicrobial activity, we focused on 3, namely: Ciprofloxacin; (+)-Usnic acid; polyhexamethyle biguanide (PHMB).

2. Materials and Combinations Developed—We developed six different compositions of the biomaterials in both Elvax and polyurethane (Table 1). Using the twelve blends [six formulations in each of the two polymers], we molded a total of 32 plaques. Over 250 punchings were made for bacteriological and cytotoxicity testing.

Solubility: The three active compounds used (ciprofloxacin, (+)-usnic acid and PHMB) have differing solubility profiles. The ciprofloxacin used was as the betaine form (free base) and has a solubility of 79 µg/mL in water [22]. The HCl salt of ciprofloxacin increases its solubility by at least 10 times. (+)-usnic acid has a solubility limit of 32 µg/mL in water. NaOH was found to increase the solubility of (+)-usnic acid to a maximum solubility of 153 µg/mL at pH 12 [23]. PHMB is extremely water soluble when used in the hydrochlorides form.

Solvents: Distilled water is the preferred solvent for UV-vis analysis of all three antimicrobials to simulate the ear environment and to minimize experimental interferences. As further described below, this was carefully done because of the differing and often low solubility limits, interference with absorption peaks, and potential swelling of the polyurethane. Organics solvents such as methylene chloride and acetone were tried in an attempt to improve solubility, but resulted in poor UV-vis spectra and obscuring absorption peaks due to the solvent. Changing the pH also created problems because low pH increases cipro solubility, but high pH increases (+)-usnic acid solubility. Changing the pH also

created salts that changed the absorption peaks and may likely change the release kinetics. Hence, neutral solutions were used in the study.

Bacterial Strains and Growth Medium—We used the four pathogens (species) most commonly isolated from post-tympanostomy tube otorrhea (P-TTO), namely: *Pseudomonas aeruginosa* (P. aer), *Staphylococcus aureus* (S. aur), *Haemophilus influenzae* (H. inf) and *Streptococcus pneumoniae* (S. pne). P. aer and S. aur. were grown on brain-heart infusion (BHI) broth or agar (Oxoid Ltd. UK). H. inf was grown on BHI, supplemented with Haemin and B-NAD, and S. pne was grown on Todd-Hewitt Broth (THB) or plated on Tryptic Soy Agar plates with 5% sheep red blood cells (TSA-BA). All *in vitro* incubations were conducted at 37°C with 5% CO₂ in a humidified incubator.

2.2. Methods

a) Melt Blending into Elvax and PU—With the eventual goal of making ear tubes by mass production methods, such as injection molding, it was necessary to develop reliable methods to pre-blend the active ingredients into the viscous molten polymer. The principal equipment used was a Brabender Model 1200 Plasticorder [C.W. Brabender Inc., So. Hackensack, NJ] with a mixing chamber of 45 cc capacity and adjustable rotational speed and melt temperature. Typically, the polymer pellets were melted or “fluxed” at a temperature 40°C (or more) above their melting temperature to lower the melt viscosity to a range suitable for blending the active compounds listed in Table 2.

Release Kinetics Methods—The objective is to study the release kinetics of the antimicrobial additive(s) ciprofloxacin, (+)-usnic acid, and PHMB, and their combinations, from two polymer hosts, namely, polyurethane (Pellethane 2363-90AE) and an ethylene-vinyl acetate copolymer (Elvax 560, which contains 15% or more of vinyl acetate), to develop a new class of antimicrobial and antibiofilm materials for use as TTs.

Wash pretreatments: Experiments were performed with and without pre-washing the as-processed materials/coupons to measure the effect of such pre-washing step on the initial release bursts. A large excess of distilled water (500mL water per sub-gram samples) was used to wash the coupons. In other experiments, 5-minute rinse with 10% acetone was used to wash the materials to remove excess (+)-usnic acid that may have bloomed to the surface during processing.

Experimental Design: Discs or squares of polymer sheets with a 1/16” nominal thickness and ca. 1/2” diameter were used in our testing. The disks were placed in disposable sample vials with 5ml (for short-term studies) or 15 mL (for long-term studies) of distilled water. Racks of vials were agitated daily. For short-term studies, the solutions were replaced after each measurement, and the measurement was adjusted for the time between measurements. A Beckman DU-530 UV-vis spectrophotometer was used to measure release rates of ciprofloxacin, (+)-usnic acid, and PHMB from the polymers. A standard 3.5 mL quartz cuvette was used and was rinsed with distilled water between samples. After solvent optimization, (+)-usnic acid was measured at 222nm, PHMB was measured at 240nm, and ciprofloxacin was measured at 322nm.

Data Analysis: The solution in contact with each of the samples was placed in the cleaned cuvette and measured in the UV-vis spectrophotometer. The peak heights were measured and corrected for the baseline and the control polymer. Concentrations of the antimicrobials in µg/mL were calculated from absorbance through least square linear fits of calibration curves. Each equation had a fit of at least R=0.99 or better.

Minimum Inhibitory Concentration (MIC)—We measured the MIC of the four pathogens using a conventional assay. Briefly, overnight cultures were diluted to a concentration of approximately 10^5 CFU/ml in the appropriate medium containing a dilution series of (+)-usnic acid (UA), ciprofloxacin or PHMB. The culture was incubated overnight at 37°C. The break point concentration at which the culture did not grow was determined from the optical density (OD) measured in a plate reader. For *S. aureus*, we also included the light emitting lux strain RN 4220, since we wished to utilize the IVIS Imaging System for the detection of biofilm formation by light measurement. The experiment was performed in duplicate. All of the strains were sensitive to ciprofloxacin. The Gram positive strains of staphylococcus and pneumococcus were sensitive to (+)-usnic acid, which is known to inhibit Gram positive bacteria [24], as well as PHMB. *P. aeruginosa* was insensitive to (+)-usnic acid and relatively insensitive to PHMB. Interestingly, *H. influenzae* II, a Gram –ve organism, was moderately sensitive to (+)-usnic acid and PHMB.

3. Results and discussion

The results of kinetic measurement are presented on Fig. 3 and Fig. 4 separately for Elvax and polyurethane materials, respectively.

It is clear from the results that the nature of the polymer host strongly affects the magnitude of drug release, and this influence is different for the drugs/compounds used in the study. In particular, the use of polyurethane provides stronger release for usnic acid compared to the Elvax case. On the contrary, polyurethane is not valid for providing sufficient release for both Ciprofloxacin and PHMB.

The results also show that the influence of drug nature on the magnitude of release may even be stronger than that of polymer. PHMB release is weak in both Elvax and Polyurethane. The usnic release is stronger in comparison to other drugs in both Elvax and PU. The importance of the polymer host selection is clearly seen in the ciprofloxacin case; namely, polyurethane is not as favorable for the ciprofloxacin case. Whether the achieved magnitude of drug release is valuable or not for OM treatment becomes clear after comparison with minimum inhibition concentrations. The results of their measurements are presented in Table 3.

The above table demonstrates a large difference of bacteria response to different antibiotics/antimicrobial compounds. The comparison of the release kinetics curves show that PHMB is not valid compound for release and for OM treatment. The high MIC value in usnic acid case with respect to *P. aerogenosa* leads to the conclusion that usnic is not very effective with this microorganism as well. On the contrary, comparison of the release kinetics curves for ciprofloxacin in Elvax case with Table 3 data leads to the conclusion, that the cipro/Elvax blend may be a good candidate for OM treatment when used as TT. With respect to ciprofloxacin, a question arises regarding how long will ciprofloxacin released from the TT implant be able to effectively suppress bacterial growth in the middle ear. To address this question, reliable interpretation of the measured kinetic curve of drug release will be necessary.

The measured release kinetics curves revealed two stages of antibiotic release. During the first stage of fast release, the rate is almost invariant and is determined by the diffusion through the steady diffusion layer formed due to solution agitation. In this first stage, the influence of the initial internal transport from the implant is weak because it occurs at a negligibly small distance from interface and accordingly at a negligible concentration drop. After the antibiotic concentration decreases within much broader layer of matrix near interface, the internal transport becomes important. This manifests itself as the second stage

in measured kinetics of release which is characterized by a significant and gradual decrease in the rate.

The short-term drug release during 6 days provides antibiotic concentration above the minimum concentration of inhibition. Unfortunately, the rate of long term release decreases significantly and becomes insufficient to provide protection against infections and recurrence of OM after 6 days. This result directed our attention to the theory of release from monolithic disperse polymeric system in an effort to understand how to enhance long-term release of the antibiotics from the implant.

Our two-stage kinetic curves for usnic acid release from Elvax provided reasonable good agreement with the generalized Higuchi equation (Fig. 5).

On the contrary, for the cipro/Elvax and cipro/polyurethane cases, with much slower second stage release, we found that the generalized Higuchi equation does not work. It turned out that the generalized Higuchi equation causes a constraint on the inter-relationship between 4 main measurable characteristics of the two-stage kinetics curves. Our experimental data do not meet this constraint.

The short term release is characterized by its duration T_1 and the released mass $M(T_1)$. The long-term release is characterized by total time of release T_1+T_2 and the total mass of released, $M(T_1+T_2)$. The application of the generalized Higuchi equation leads to a constraint on the relationship between these 4 measurable characteristics:

$$\frac{M(T_1+T_2)}{M(T_1)} > \sqrt{\frac{(T_1+T_2)}{T_1}} \quad (13)$$

The experimental curves from Roseman and Higuchi [13] satisfy these constraints. Our experimental data do not satisfy this constraint.

Our analysis revealed that an essential limitation is inherent to the Higuchi model. In this model, it is assumed that the first drug dissolution stage is infinitely rapid and that the subsequent diffusion process controls the drug release. Later theories by Ayres and Lindstrom [25,26] have shown that models based on instantaneous dissolution provided a good description of the release kinetics only when the drug dissolution proceeded rapidly in comparison with diffusion process.

As soon as a finite dissolution rate is accounted for, the release kinetics become dependent on the initial specific surface area A_o of the drug, or the particle dimension, which arises in the expression for dimensionless dissolution rate

$$\kappa = KL^2 A_o / D \quad (14)$$

where K is dimensional dissolution rate.

The theory of Ayres and Lindstrom is rather difficult to apply for experimental interpretation. On the other hand, Frenning's theory [27] is supplemented by graphs, which illustrate well the influence of κ or A_o on the release rate. The figures from Frenning's theory are provided for illustration in Fig. 6.

In Fig. 6, the Higuchi equation is expressed by the dotted straight line because the square root of time is present on the abscissa axis. Frenning's curve almost coincides with Higuchi

curve, when κ or A_0 are large, i.e., at large surface area the dissolution stage is very rapid and does yet affect release. However, the smaller κ or A_0 (smaller dissolution rate) the smaller is the release rates are predicted.

At sufficiently large drug particle dimension, the release rate decreases with the increasing particle size. A similar regularity may arise due to particle aggregation. It is obvious that the dissolution rate of aggregate decreases with the increase of its dimension. During preparation of polymer-drug blend by extrusion, aggregation occurs during mixing.

Our microscopic inspection of the specimens (Cipro/Elvax, Cipro/polyurethane, Elvax/Usnic) revealed a significant drug aggregation. Aggregation of drug particles caused the systematic decrease in the long-term release in our study. Analysis of our data was confirmed by approximate estimate with the Frenning theory [27].

Conclusions and future directions

Polymer-drug blends were formed by melt processing for application as TT. The release kinetics of drugs release was tested and compared with the minimal inhibitory concentration (MIC) for antibiotics for 4 bacterial species implicated in otitis media. The release rate is fast during the first release stage and essentially exceeds MIC for the case of ciprofloxacin which was sufficient for preventing bacterial growth and biofilm formation on TT materials during at least 6 continuous days. The further significant retardation of the drug release after the first 6 days may be caused by the slow rate of the kinetics of drug dissolution. This harmful effect was found to increase with the aggregation of drug particle and was confirmed in our case. Melt processing of polymer and particulate drugs causes the condition for drug particle aggregation. Therefore, close attention has to be paid to particle aggregation which is inherent in melt blending to minimize the concomitant decrease in the release rate.

The achieved understanding of the release rate retardation will allow us to enhance the second stage of ciprofloxacin release which in turn will extend the time during which recurrent infection of the middle ear may be prevented during the long-term use of TT.

In related studies, we consider that the transport of the released antibiotics from TT to the surface of the middle during inflammation takes place via the exudates which fills portion of the middle ear or by an exudates liquid film which covers its surface just before an infection occurs. The random film flow as well as the random exudates circulation, when it fills the entire middle ear enhance the diffusion transport of the antibiotics and decrease the antibiotics losses in the surrounding tissue. This mechanism may achieve concentrations higher than the MIC necessary for the suppression of bacteria penetrating into the middle ear through Eustachian tube. With the purpose of this prediction the modeling of exudates circulation caused by inertial forces concomitant to random head movement and film flow due to gravity will be accomplished. The coupling the antibiotic release and its random convective transport during random head movement constitutes a new direction in the development of controlled drug release from implant for use in otological implant such as in the middle ear.

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Higuchi (model)

Fig. 1.
Illustration of Higuchi's model.

Fig. 2. Schematic diagram of the concentration profile in polymer matrix containing dispersed drug and an adjacent stirred solution in receiving chamber.

Fig. 3.
Experimental curves for the kinetics of drug release in the case of polymer/drug blend using Elvax host polymer.

Fig. 4. Experimental curves for the kinetics of drug release in the case of polymer/drug blend using polyurethane host polymer.

Fig. 5.

The release kinetics in the usnic/Elvax case. 1 – experimental curve; 2 – fitting the experimental curve using the Higuchi generalized equation.

Fig. 6.

Fractions of released drug calculated for (a) $C_s/C_0 = 0.01$, (b) $C_s/C_0 = 0.1$, and (c) $C_s/C_0 = 1.0$. The solid lines show the result of the numerical calculations and the broken ones are calculated according to the analytical short-time approximation. For each value of C_s , the calculations were performed from left to right in each graph, $\kappa=100$, 10, and 1.0. The dotted line in each graph is calculated according to the modified Higuchi formula [27].

Table 1

Polymer blend compositions.

Composition	Polymer host only	Usnic	PHMB	Cipro	Cipro + Usnic	Cipro + Usnic + PHMB
Loading (weight %)	Control	3%	3%	3%	3% each	3% each

Table 2

Antibiotics, antimicrobials and host polymers used in this study.

Compound	Common Name	T _m (°C)	Source
Ciprofloxacin	Cipro	257	Fluka
(+)-Usnic Acid	Usnic	203	Sigma-Aldrich
Vantocil B	PHMB		Arch Chemicals
Polyurethane	Pellethane™ 2363 90AE PU	89*	Dow Chemical
Poly(ethylene-vinyl acetate)	Elvax® 560	69*	DuPont

* Vicat softening temperature

Table 3

Minimum Inhibitory Concentration (MIC) of the three proposed antimicrobials against four pathogens implicated in otitis media

	P, aer	S. aur GFP	S. aur-lux	H.inf	S.pne
Cipro µg/ml	0.09	0.28	0.28	0.06	0.75
Usnic µg/ml	1024	4.0	3.0	16	3.0
PHMB µg/ml	48	4.0	3.0	16	6.0