

RELEASE CHARACTERISTICS OF IMPLANTABLE MULTIPLE-HOLED
CUBICAL MATRICES

İMLANTE EDİLEBİLEN ÇOK-DELİKLİ KUBİK MATRİKSLERİN SALIM
ÖZELLİKLERİ

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A fabrication procedure was presented for producing implantable cubical low density polyethylene matrices which were uncoated and coated with a thin impermeable film and a thick paraffin layer leaving a hole on the surfaces of the cubes. Drug matrices were prepared by directly compressed sodium salicylate and polymer blended into an appropriately designed mold which was made of stainless steel at 150°C. Zero order drug release was obtained from covered matrices. The geometrical relationship between the cube and the hemispheres was investigated in terms of diffusion principles. These results suggested that the drug release was controlled by imaginary hemispheres existing in the cube. The amount of constant drug release could be increased by using multiple-holed cubic systems.

Bu çalışmada, implante edilebilen kaplanmış ve yüzeylerindeki bir delik hariç olmak üzere ince ve geçirgen olmayan bir film ve kalın bir parafin tabakasıyla kaplanmış kubik, düşük dansiteli polietilen matrikslerin imalatı için bir fabrikasyon yöntemi sunulmuştur. İlaç matriksleri, paslanmaz çelikten uygun şekilde imal edilmiş bir kalıp içine sodyum salisilat ve ilaç karışımının direk basılması ile hazırlanmıştır. Küp ve yarım küre arasındaki geometrik ilgi difüzyon prensipleri açısından incelenmiş ve elde edilen sonuçlara göre ilaç salımının küpte bulunan sanal yarım küreler tarafından kontrol edildiği ileri sürülmüştür. Böylece sabit ilaç salımının çok-delikli kübik sistemler kullanılarak artırılacağı anlaşılmıştır.

Keywords: Implantable cubical matrices; Low density polyethylene; Fabrication procedure; Zero order drug release; Geometrical shape control

Anahtar kelimeler: Implante edilebilen kubik matriks; Düşük dansiteli polietilen; Fabrikasyon yöntemi; Sıfırıncı derece ilaç salımı; Geometrik sekille kontrol.

Introduction

Recently, some authors were concerned about the relationship between the geometrical shape and drug release from different systems such as spherical, cylindrical, circular cylindrical, planar, biconvex, square, clover leaf and cross (1-9).

However, this relationship was proved only for circular cylinder system that achieve zero order kinetics (8,9). Hsieh et al. claimed that the drug release rate from the circular cylinder system was initially high, but not achieving linearity at the end (10). One of the special shapes evaluated for a constant drug release was a tablet form with a central hole (11-14) and the

other one was a hemisphere dosage form with the surface covered with an impermeable coating except for a small cavity at the center of the flat surface (10,15,16). Recently, we presented a cylindrical polyethylene device which was coated with a thin impermeable film and a thick paraffin layer with a hole on the flat surfaces from which a constant drug release was observed (17). Furthermore, a multiple hole system distributed uniformly on an impermeable membrane was presented in order to increase the constant drug release (18). In the present study, a new cubical implant made of low density polyethylene and sodium salicylate

containing a central hole on the surface was prepared using a stainless steel mold at 150°C to increase constant drug release. Calculations were performed for the geometric structure with effective diffusion controlled part of implants and it was found that the behavior of drug release from matrices in saline solution was similar to the imaginary hemispheres existing in the cube. There are six imaginary hemispheres and an uncontrolled part between these hemispheres in the cubical matrix (Fig. 1). If the cube is covered with an impermeable layer except for the holes on the surfaces, drug will diffuse only through these holes in the solutions.

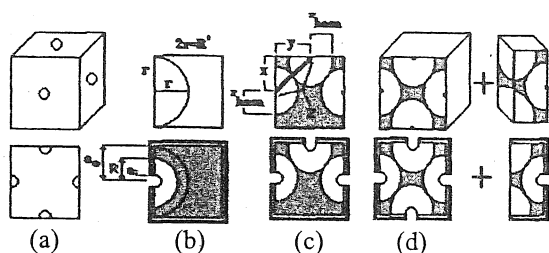


Fig. 1. The illustration of the imaginal hemispheres in the cubical devices. Cross sections of (a) uncovered device; (b) one-hole covered device; (c) three-hole covered device and (d) five-hole covered device. The cross section of the one hole device at time t is given in the lower part of (b)

Information on drug diffusion from covered hemispheric matrices were mentioned in a recent study (10).

Fick's law of diffusion is $dQ/dt = -DAc/dr$ (Eq.1) where Q is the mass of drug being transformed, t is the time, c is the drug concentration, D is the diffusion coefficient (constant), A is the area for mass transport and r is the distance from the diffusion source to the release surface. It can be seen in Fig. 1-b that when r increases, drug release also increases by virtue of the increase in the available diffusion area due to the geometric

structure to compensate for the increase in diffusion distance of drug transport. Then the release rate for the hemisphere can be derived from the equation mentioned below: $dQ/dt = 2C_s D a_i (R / R - a_i)$ (Eq. 2) where C_s is the drug solubility in the release media, a_i is the inner radius of the cavity and R is the radial distance to interface between dissolved and dispersed drug within the matrix.

The approach to zero order kinetics can be observed when $R \gg a_i$, $R - a_i$ becomes equal to R ($dQ/dt = 2Dc_s a_i$) (Eq. 3). Each of the terms in Eq. 3 is a constant. Thus for a hemispheric device with small a_i , release rate will essentially be constant. Then, Kuu and Yalkowsky (18) derived the Eq. 3 mentioned below for multiple-holed membrane systems, $dQ/dt = 2N\pi D a c_s$ (Eq. 4) where N is the total number of holes on the device and $a = a_i$, diffusion area of a hemisphere with a_i radius, is $A = \pi 2a_i \cdot 2a_i/2$, so the diffusion rate from a covered hemisphere will be as follows $dQ/dt = 2D c_s \pi a_i^2$ (Eq. 5). This equation can be used for our one hole covered cubical matrices. For three and five-hole cubes, the components of this equation must be multiplied by 3 and 5 respectively

$$(dQ/dt = 2Dc_s \pi a_i^2 \times 3 = 6Dc_s \pi a_i^2 \quad (\text{Eq.6}),$$

$$(dQ/dt = Dc_s \pi a_i^2 \times 5) = 10Dc_s \pi a_i^2 \quad (\text{Eq.7})$$

Volumetric evaluations of imaginary hemispheres in the cubical matrix:

The volume of a cube and a hemisphere can be found from Eq. 8 and Eq. 9, respectively.

$$V_{\text{cub}} = R^3 \quad (\text{Eq. 8})$$

$$V_{\text{hem}} = 4/3\pi r^3/2 \quad (\text{Eq. 9}).$$

If R' is accepted as 1 ($R' =$ one edge of cube. Fig. 1-b), r will be 0.5 and the equations will become; $V_{\text{cub}} = 1 \text{ cm}^3$ and $V_{\text{hem}(1)} = 0.262 \text{ cm}^3$ thus, the percent of a hemispheric volume in the one-hole cube

will be: $(V_{\text{hem}(1)} / V_{\text{cub}}) \times 100 = 26.2\%$ For the three-hole devices, the hemispheric volume can be calculated from the concept dealing with the right triangle (Fig. 1-b) and: $x^2 + y^2 = z^2$ (Eq. 10) where $x = y = 0.5$, $0.25 + 0.25 = z^2$, $0.5 = z^2$, $z = 0.708$, $z/2 = r_{\text{hem}(3)} = 0.354$ and $V_{\text{hem}(3)} = 4/3 \times 3.146 \times 0.354^3 / 2 = 0.092 = 9.2\%$ and the percent volume of 3 hemisphere is; $9.2 \times 3 = 27.6\%$ (Fig. 1-c), and 5 hemisphere is $9.2 \times 5 = 46\%$ (Fig. 1-d).

Materials and Methods

Sodium salicylate (Paninkret Co., Westerhom, Germany), (BP 1993), and low density polyethylene (Pet-Kim Co., Izmir, Turkey) ($d=0.921$). Sodium chloride, (Merck Co., Darmstadt, Germany). Impermeable film used for the first covering of the matrices was made using Uhu[®], Colle Universale, manufactured in Turkey under license of Ligner & Fischer GmbH, 7580 Buhl, Germany. Analytical grade paraffin was used throughout the study.

Preparation of Cubical Matrices

Sodium salicylate and low density polyethylene were passed through a 40 mesh screen prior to usage. 30% of sodium salicylate and 70% of polyethylene were mixed together in a cube blender for 5 minutes. Then a hollow cube mold was loaded with 1.10 g of this drug-polymer blend and placed into an oven preheated to 150°C. After 30 minutes, a steel plunger was forcefully inserted into the mold. By using this type of mold to compress the polymer-drug matrix, a small cavity was formed on the flat surfaces of the cubical matrix. After compression, the mold containing the cubical matrix was cooled to room temperature. The mold was then disassembled and the matrix was removed. To protect the cavity within the cubical matrix during coating, a steel bead (2 mm Ø) was inserted into it. The outer surface area of the cubical matrix was then coated with a thin film using a brush, after which the device is plunged into paraffin at 60°C for the following paraffin coating. Finally, the steel bead was removed from the cavity (Fig. 2,3).

In vitro dissolution studies

The cubic matrices were placed in a vial containing 10 mL saline. The vials were men

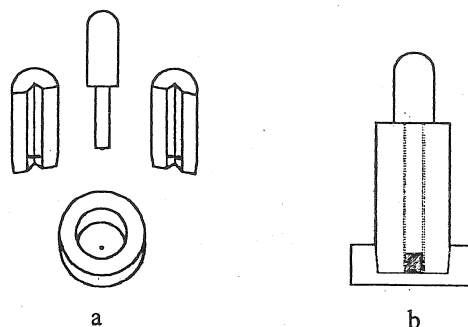


Fig. 2. The steel molds and plunger for making cubical devices; (a) Separate position and (b) Cross section of working position.

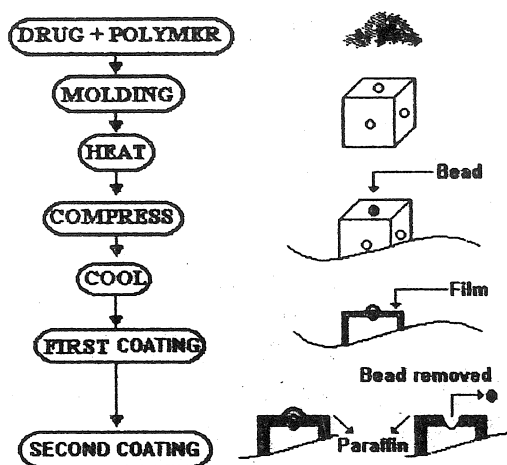


Fig. 3. Production steps of covered cubical devices

placed onto a shaker (20 shakes per minutes.) at $37 \pm 1^\circ\text{C}$. At each time intervals, 10 mL dissolution medium was transferred to a tube and 10 mL - fresh saline was added into the vial. The spectrophotometric (UNICAM 8625 UV/VIS Spectrophotometer) assay of sodium salicylate was conducted at 294 nm for each sampling.

Kinetic evaluations

The results obtained from dissolution studies were evaluated kinetically by $(Bt)^n$, first order, zero order, Hixon-Crowell, RRSBW, $Q\sqrt{t}$, Higuchi, Hopfenberg spherical, Hopfenberg cylindrical and Hopfenberg slab equations (19-27). The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated evaluated by a means of a computer program (28) and the best kinetic model was selected.

Results and Discussion

The equation of the standard curve of sodium salicylate was as follows:

$$y = 44.753 x - 5.915 \quad (r = 0.999)$$

The sensitivity of the method was within the range of 1-12 $\mu\text{g/mL}$ of drug concentration. The length of the edges, the weight and the density of the prepared cubic matrices were $1\text{cm} \pm 0,1 \text{ cm} \pm 0, 1.026\text{cm} \pm 0.008 \text{ (SE)}$, $0.979\text{g} \pm 0.008 \text{ (SE)}$ and $d=0.955 \pm 0.014 \text{ (SE)}$ respectively.

The cumulative drug release profiles of the slabs and coated matrices are shown in Fig. 4. It is obvious that the release of the uncoated cube was more rapid than the coated ones and as the number of holes increased, the drug release was also increased into the coated matrices. Normally, the longest release time was observed from one holed device because of the slowest drug release. Drug release continued for 35, 62, 50, 35 days for uncovered, one, three and five-holed devices respectively so the amount of drug released and releasing time of the implanted drug could be adjusted according to needs. Essentially, the drug release continued after these days but we ended the sampling when the drug concentration in the test solution fell below 0.1 mg/mL. It was concluded that the RRSBW distribution was the best model for the release profile of uncovered matrices (Fig. 5)

The cumulative drug release profile of one-hole coated matrices are shown in Fig. 4. Zero order drug release was observed for the first 4 days and then drug release continued according to the RRSBW distribution (Fig. 6). This dual release profile was conformed by the coated one-hole cubic device which had an imaginary hemisphere. A constant drug release was observed only when drug

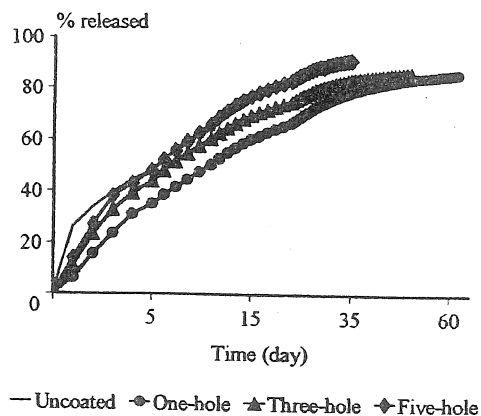


Fig. 4. Cumulative percent drug release from uncoated and coated cubical devices (n=3)

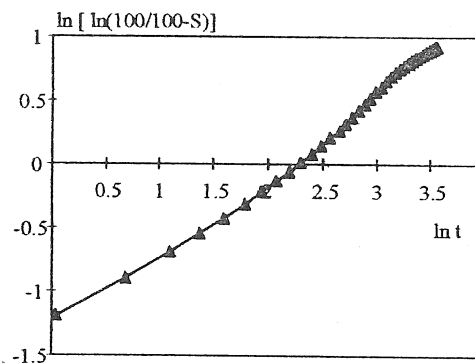


Fig. 5. RRSBW distribution of uncoated cubical devices ($r^2 = 0.986$)

release was from the hemisphere. In this case a constant release was not expected for the rest of the dissolution. 3.8% of drug amount and 0.6 day differences were found between practical and theoretical drug releases (Fig. 7).

As for the three-hole devices, a constant release was seen for the first 3 days of dissolution and 32.6 % of the drug content of matrix was released (Fig. 8). The RRSBW distribution was also observed for the rest of the dissolution similar to the one-hole device. Approximately 5% of drug amount and 0.4 day difference was shown between the

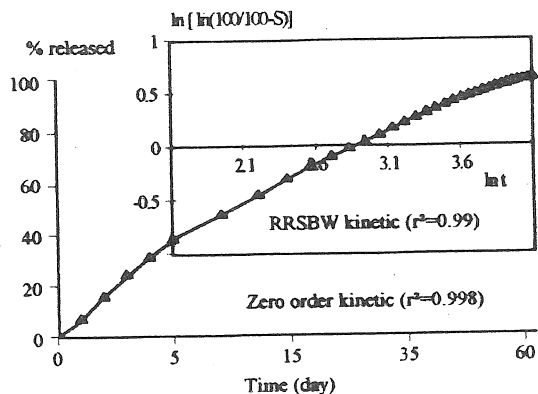


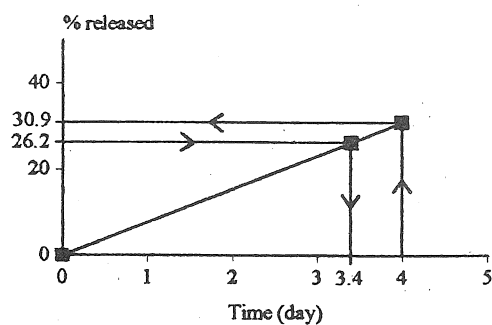
Fig. 6. Two steps kinetic distribution for drug release from one-hole device

practical and theoretical drug release from the device (Fig. 7).

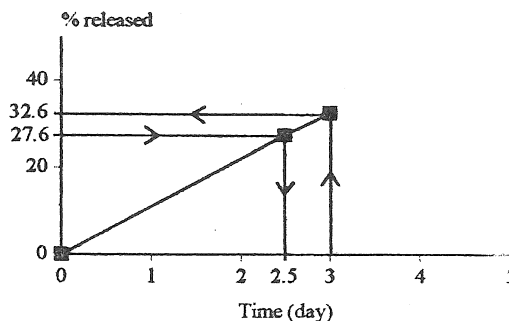
For the five-hole devices, a constant release was seen for the first 3 days of dissolution and 38% of the drug content of matrix was released. There were some differences in drug amounts and days and these were 1.4% and 0.2, respectively (Fig. 8,9).

In conclusion, the cubical devices were produced by fabrication procedure for the first time in this study. This procedure was simple, useful and the products were reproducible. The matrices prepared were covered with two layers contradicting with some articles (10, 29). If the upper layer was broken or fissured, the second layer could still guarantee the function of the system. From this point of view, this system was reliable and very resistant to external effects.

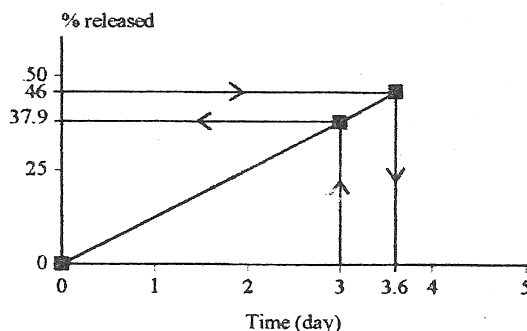
The results of the dissolution studies confirmed of imaginary hemispheres consisted in the cube because a constant drug release was observed from the hemispheres. The behavior of the drug release from cube in 0.9 % of NaCl was shown with a two step kinetic distribution. The first step was zero order and the second step was RRSBW kinetic model.



(a)



(b)



(c)

Fig. 7. Comparison of the theoretical and practical drug release (a) from one-hole device; (b) from three-hole device and (c) from five-hole device

Although, various geometric shapes had been trained to obtain a zero order drug release for the matrix systems, a good constant release was achieved with only some special devices such as holed-

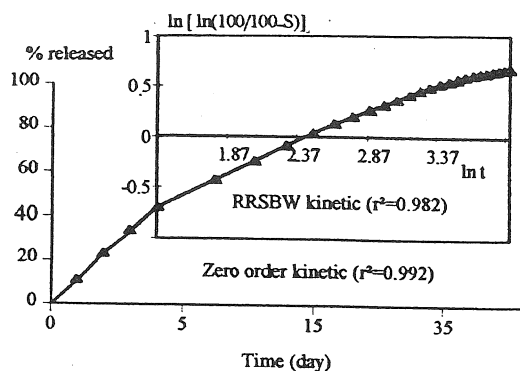


Fig. 8. Two steps kinetic distribution for three-hole device

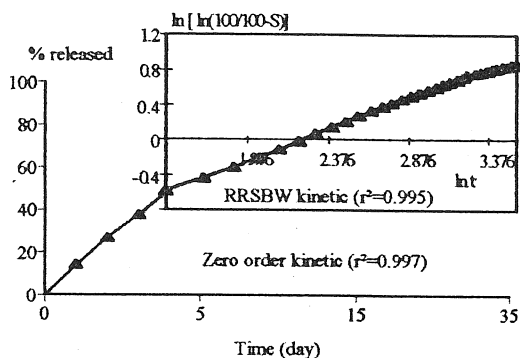


Fig. 9. Two steps kinetic distribution for five-hole device

hemispheres (10, 15) and holed-tablets (11-14). Kuu and Yalkowsky (18) described an approach to near zero order drug delivery system that utilizes a device consisting of multiple holes uniformly distributed on an impermeable membrane. Drug release was increased with the number of the holes in this system. In our study, multiple-holes were distributed in the middle of the surfaces of a cube to prevent the expanding of the system so matrices could be used as an oral dosage form using appropriate polymer and covering material. The amounts of drug released from matrices in the first day were 6.2, 10.7, 13.9 and 23.8 mg for one-hole, three-hole, five-hole and uncovered device respectively. Essentially, the

amount of release from three and five-hole devices was three and five fold more than that of one-hole device but the drug release from one hole device was faster than we expected.

Cubic system was devised for dispensing more than 1 mg. drug day by implantation. Implants could be used by eroding the sharp corner and length of the cubic matrix for painless application. Release profiles would not be affected greatly from this procedure.

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