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In Vitro Programmable Implants for Constant Drug Release

Sabit İlaç Salımı İçin İn vitro Programlanabilen İmplantlar

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Abstract

In this study, the relationship was investigated between the drug release and the geometric shapes of covered cylinders and hemicylinders which were employed as controlled release systems This relationship was proven by mathematical calculations and dissolution results in terms of diffusion principles for matrix systems. Therefore, a fabrication procedure was demonstrated of producing implantable holed cylindrical and hemicylindrical low density polyethylene matrices which were uncoated and coated with a thin impermeable film and a thick paraffin layer except a channel on the flat surface of the implant. Implants were prepared by directly compressed sodium salicylate and polymer blend into an appropriately designed stainless steel mold at 150°C. Zero order drug release was obtained from covered both cylindrical and hemicylindrical implants. The drug release could also be controlled by adjusting of the matrix's length.

Key words: Sodium salicylate, polyethylene, constant drug release, implant, geometric shape.

Introduction

The effect of geometric shape of a dosage form on the drug release, especially to achive a constant release, has taken the interest of many researchers (Rippe and Johnson, 1969; Roseman and Higuchi, 1970; Roseman, 1972; Cobby *et al.*, 1974a; Cobby *et al.*, 1974b; Brooke and Washkuhn, 1977; Lipper and Higuchi, 1977; Rhine *et al.*, 1980; Bechard and McMullen, 1988; Marentette and Grosser, 1992; Siepmann *et al.*, 2000).

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For this purpose, the special tablet forms with a central hole (Hsieh *et al.*, 1983; Hansson *et al.*, 1988; Sangalli *et al.*, 1994a; Sangalli *et al.*, 1994b; Sangalli *et al.*, 2003) and hemisphere dosage form with the surface covered with an impermeable coating except for a small cavity at the centre of the flat surface were presented (Hsieh *et al.*, 1983). Recently, we have developed polyethylene cylindrical (Ertan *et al.*, 1997) and cubical (Karasulu *et al.*, 2000) implants which were uncoated and coated except a hole on the flat surfaces of the matrices and a constant drug release was obtained. In the present study, a new holed cylindrical and hemicylindrical implants made of low density polyethylene and sodium salicylate containing a central channel on the flat surface was prepared using a stainless steel mold at 150°C to obtain both constant and programmable drug release.

Fick's law of diffusion is,

$dQ/dt = -Dadc/dr$ (Eq.1),

where Q is the mass of the drug being transformed, t is the time, c is the drug concentration, D is the diffusion coefficient. A is the area for mass transport and r is the distance from the diffusion source to the release surface. The release rate for the hemisphere can be derived from the equation mentioned below:

$dQ/dt = 2CsDa (R/R-a)$ (Eq. 2),

where Cs is the drug solubility in the release media, a 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>>a, R-a becomes equal to R and the drug diffusion rate is,

$dQ/dt = 2DCsa$ (Eq. 3).

Each of the terms in Eq. 3 is a constant. Then Kuu and Yalkowsky (Kuu and Yalkowsky, 1985) derived the Eq. 3 mentioned below for multiple holed membrane systems,

$dQ/dt = 2NDCsa\pi$ (Eq. 4),

where N is the total number of holes on the device and diffusion area of a hemisphere is,

$A = \pi 2a2a/2$,

so the diffusion rate from a covered hemisphere will be as follows,

$dQ/dt = 2DCsa^2\pi$ (Eq. 5).

The diffusion area of a channel in the shape of hemicylinder is,

$A = 2\ \pi rl/2$,

where r is the radius of the cylinder and l length of the cylinder and diffusion rate from this channel will be as follows,

$dQ/dt = DCs\pi rl$ (Eq. 6),

and diffusion rate from a both holed and covered cylinder will be as follows,

$dQ/dt = 2DCs\pi rl$ (Eq. 7), (Fig. 1).

Material and Methods

Sodium salicylate (Paninkret, Westerhorn, Germany; BP 1993), low-density (LD) polyethylene d = 0.921 (Pet-Kim, İzmir, Turkey), sodium chloride (Merck Co, Darmstadt, Germany).

Impermeable film used for the primary covering of the matrices was made using Uhu®, Colle Universale, manufactured in Turkey under license of Ligner&Fiscer GmbH, 7580 Buhl, Germany. Analytical grade paraffin was used for secondary covering of the matrices.

Preparation of cylindrical and hemicylindrical implants:

Sodium salicylate and low density polyethylene were passed through 40 mesh screen prior to usage. 30% of sodium salicylate and 70% of polyethylene were mixed together in a cube blender for 5 min. Then the hollow hemicylinder and cylinder mold was loaded with 1.25 and 2.5 g of this drug-polymer blend respectively and placed into an oven preheated to 150°C. After 30 min, a steel plunger was forcefully inserted into the mold. By using this type of mold to compress the drug-polymer matrix, a channel was formed longitudinally on the flat surface of the hemicylinderical matrices. A longitudinally hole was also formed in the middle of the cylindrical implants. After compression, the mold containing the implants was cooled at room temperature. The mold was then dismantled and the implant was removed from the mold. To protect the hole in the cylinder and the channel on the flat surface of the hemicylinder during the coating, a steel stick was inserted both into hole and channel. The implants were first coated with a thin film by use of a brush and they were plunged into paraffin at 60°C for coating, then cooled 1 h and the steel stick was removed (Fig. 2). The length of matrices prepared is 1cm.

In vitro dissolution studies:

The implants obtained were placed in a vial containing saline solution. The vials were then placed on a shaker (20 shakes per min) at 37±1 °C. After fixed time periods, the dissolution medium was transferred to a tube and 10 ml fresh saline was added into the vial. The spectrophotometric (UNICAM 8625 UV/VIS Spectrometer) assay of sodium salicylate was performed at 294 nm for each sampling.

Matrix types:

Two types of cylindrical and hemicylindrical matrices were prepared. The height and diameter of matrices were measured by use of callipers (calliper gauge, direct reading, 0.1 mm). The density (d), surface area (S) of the matrices were calculated by use of well known equations (Eq. 8-12).

$V\ (cylinder) = \pi r^2 \times h$ (Eq. 8)

$V\ (hemicylinder) = \pi r^2 \times h / 2$ (Eq. 9)

$d = M / V$ (Eq. 10)

$S\ (cylinder) = 2\pi r^2 + 2 \pi r \times h$ (Eq. 11)

$S\ (hemicylinder) = \pi r^2 + \pi r \times h + 2r \times h$ (Eq. 12)

The adjusting of the release amount:

The drug amount released (J) could be adjusted by the way of adjusting the hemicylinder's length (l). The length of the hemicylinder can be calculated according to the following equation.

$l = J / 2DCs\pi r$ (Eq. 13)

Kinetic evaluations:

The results thus obtained from dissolution studies were evaluated kinetically by zero order, first order, Hixon-Crowell, RRSBW, Higuchi, $(Bt)^a$, $Q\sqrt{t}$ and Hopfenberg equations. The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a software (Ege *et al.*, 2001).

Results and Discussion

The equation of the standard curve for sodium salicylate was y = 43.403x + 0.044 (r = 0.999). The method is sensitive within the range of 1-12 μg / mL of drug concentration. Matrix types prepared in this study and some data on height (h), surface area (S), density (d) and matrix weights (M) are given in Table 1.

Drug release continues for 20 days for both cylindrical and hemicylindrical matrices. It is clear from Figs. 3 and 4 that beginning of the dissolution process, zero-order (r^2 = 0.998) drug release takes place for the first 6 days; drug release then proceeds according to the M.Langenbucher (r^2 = 0.998) distribution for hemicylindrical and $(Bt)^a$ (r^2 = 0.999) distribution for the cylindrical implants (Fig. 4). The theoretical amount of drug release is 23.1 mg for hemicylindrical implants and the practical amounts of this value are between 18.5 and 26.4 mg. The theoretical amount of drug release is 46.2 mg for hemicylindrical implants and the practical amounts of this value are between 42.1 and 60.5 mg. When the theoretical and practical values are compared, the theoretical drug release fits well with the practicals for the hemicylindrical implants but the practical drug release is a little high from the theoretical amount of cylinder. The reason of the high amount of practical drug release of cylinders is the lower density of the cylindric implants (d = 0.896) than hemicylindrical implants (d = 0.956). Because it is known that, when the density decreases in the polymer matrices, the drug release rate increases significantly (Ertan *et al.*, 1997).

The released amount of the drug could be adjusted by the way of adjusting of the hemicylinder's length. For example; which length of the implant should be prepared for the 8.4 mg drug release in daily. Calculations could be made using following equation.

$l = J / 2DCs\pi r$ (Eq. 13),

where, J = 8.4 mg, D = 0.067 day^{-1} (Ertan *et al.*, 1997), Cs = 1.1g, The Merck Index., (1989), π = 3.14 and r = 0.1 cm.

$l = J / 2DCs\pi r = 0.0084 / 0.067 \times 1.1 \times 3.14 \times 0.1 = 0.0084 / 0.023 = 0.36$ cm

So, for the 8.4 mg drug release, the length of the hemicylinder should be 0.36 cm.

In conclusion, the hemicylindrical implants were produced by fabrication procedure for the first time in this study. This procedure was simple, easy to apply and the products were reproducible. The matrices prepared were covered with two layers contradicting with some articles (14 Hsieh *et al.*, 1983; Hsu, *et al.*, 1992). If the upper layer was broken or fissured, the second layer could still guarantee the function of the system.

The various geometric shapes had been trained to obtain a constant drug release for the matrix systems, but a good result was obtained with only some special devices such as holed and covered hemispheres (14 Hsieh *et al.*, 1983) and holed and covered tablets (10-13 Hsieh *et al.*, 1983; Hansson *et al.*, 1988; Sangalli *et al.*, 1994a; Sangalli *et al.*, 1994b; Sangalli *et al.*, 2003). In this study, we described a new zero order drug delivery system as an implant consisting of a channel on the flat surface of the hemicylinder. The constant drug release was increased with the length of the implant.

The cumulative drug release profiles of cylindrical and hemicylindrical implants are shown in Fig. 3.

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Özet

Bu çalışmada, üzeri kaplı silindir ve yarım silindir şekilli implantlar ile bunlardan ilaç salımı arasındaki ilişki araştırılmıştır. Bu ilgi matematik hesaplamalar ve ilaç çözünürlük çalışmaları sonuçları ile matriks sistemlerden ilaç difüzyonu prensipleri açısından ispatlanmıştır. Bunun için, yarımkürenin düz yüzeyinde bir kanal hariç, önce geçirgen olmayan ince bir film ile daha sonra kalın bir parafin tabakası kaplanmış ve düşük dansiteli polietilenden yapılmış yarımsilindir ve delikli silindir şeklindeki implante edilebilir matrikslerin üretimi için bir fabrikasyon imalat yöntemi açıklanmıştır. İmplantlar, uygun olarak dizayn edilmiş paslanmaz çelik kalıp içinde sodyum salisilat ve polimer karışımının 150 °C derecede direkt olarak basılması yoluyla hazırlanmışlardır. Sıfır derece ilaç salımı kaplı silindir ve yarımsilindir şeklindeki implantların her ikisinden elde edilmiştir. İlaç salımı ayrıca matriksin boyunun ayarlanmasıyla kontrol edilebilir.

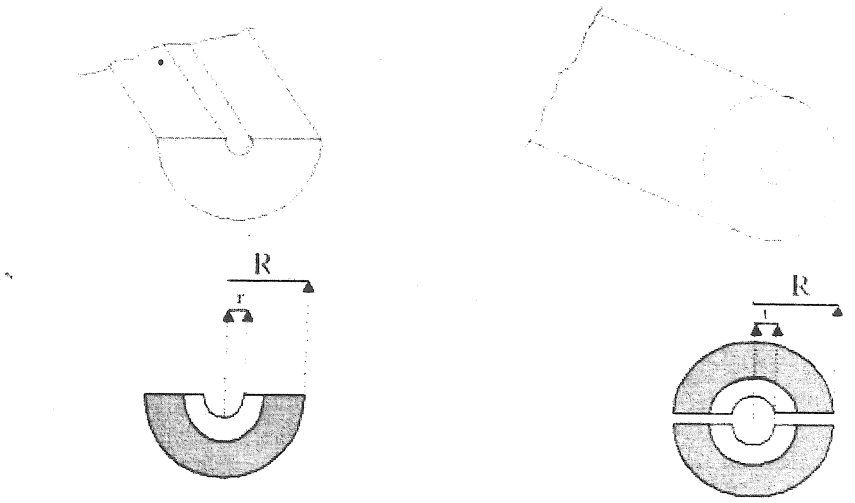
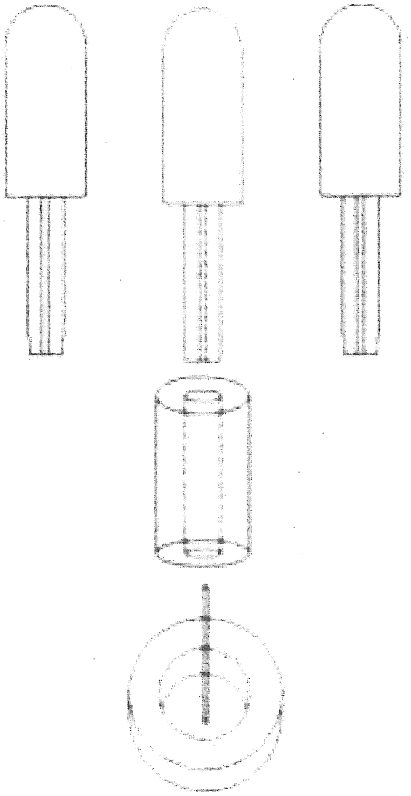


Fig. 1. The schematic diagrams and cross sections of the hemicylinder and holed cylinder and diffusion at time t.

a)



b)

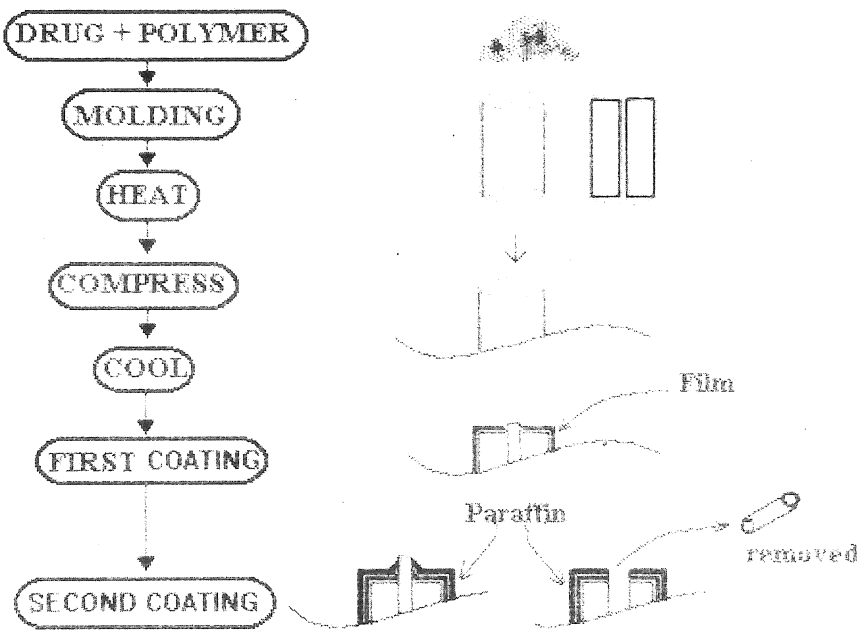


Fig. 2. The steel molds and plungers for making cylindrical and hemicylindrical implants (a) and the production steps of covered implants (b).

Table 1. Matrix types and their properties (± SE).

Matrix type	h (cm)	S (cm^2)	d	M (g)
Hemicylinder	0.96 ± 0.013	10.512	0.956	1.153 ± 0.023
Cylinder	1.06 ± 0.066	21.024	0.896	2.39 ± 0.030

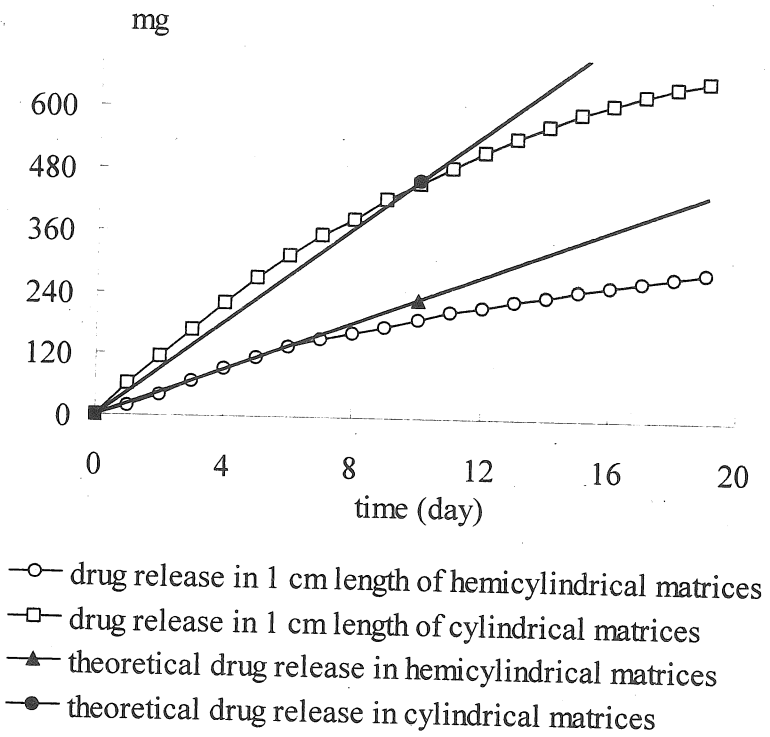


Fig. 3. The theoretical and practical dissolution profiles of the covered cylindrical and hemicylindrical matrices

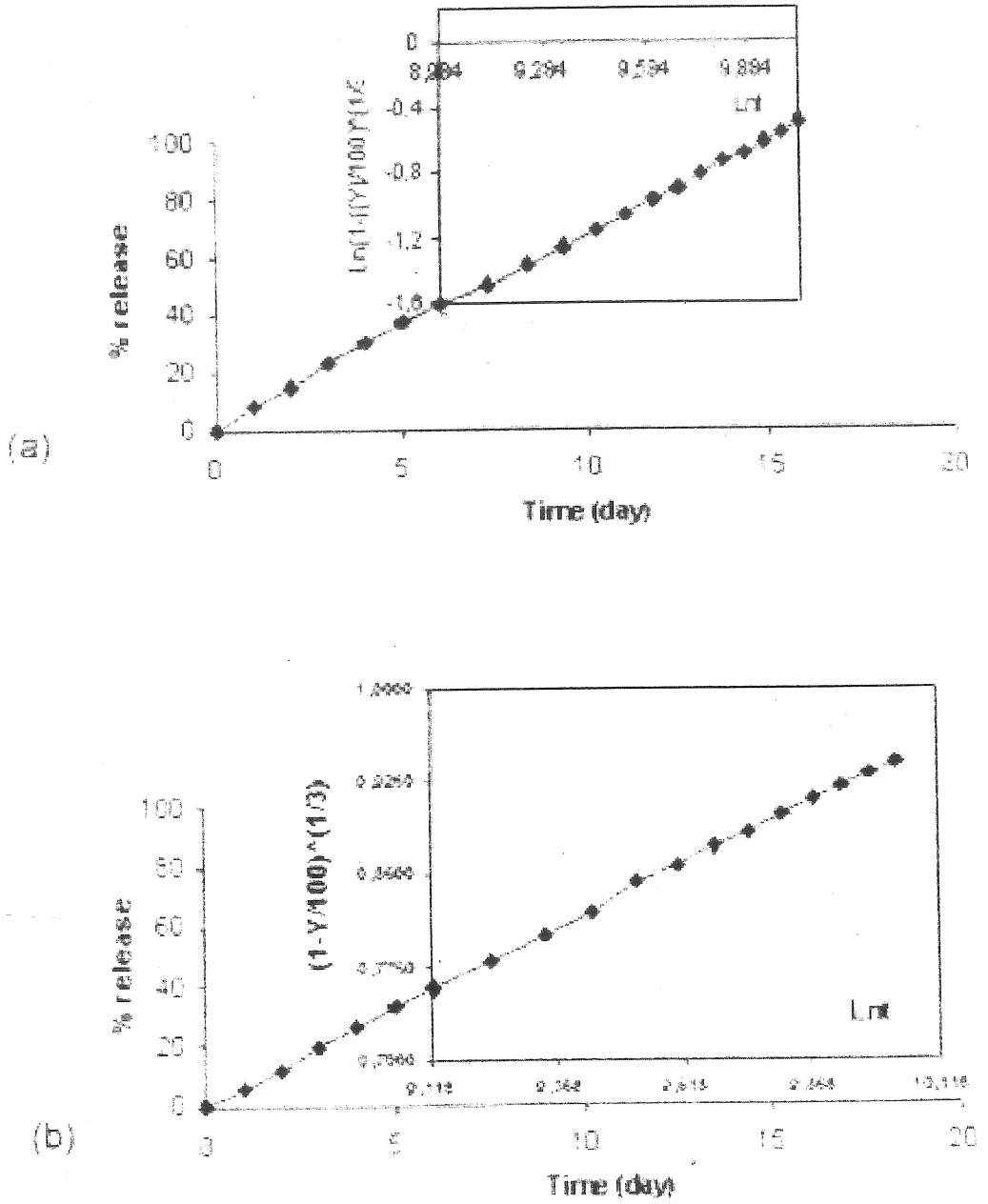


Fig. 4. The two steps kinetic distribution for drug release from covered cylindrical (a) and hemicylindrical (b) matrices

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