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INFLUENCE OF THE DRUG AND EXCIPIENT SOLUBILITY ON THE ANTIBIOTIC RELEASE FROM POLYMETHACRYLIC IMPLANTS

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A B S T R A C T

Polymethacrylic implants were prepared by use the monomer (Kallocryl^{R}) and a polymerization extrusion technique. The antibiotics used were gentamicine, streptomycine and chloramphenicol. The excipients used were amino acids with various solubilities and titan dioxyde as an inert and insoluble matrix filler. The drug release examined in vitro by use a modified pitcher/half change method was dependent on the mechanical strength of the matrix, the concentration and the solubility of the amino acid used and the drug concentration and solubility.
The water inflow into the matrix was of effect on the volume of pores and may be influenced by the drug and excipient particle size and solubility.
There was a relationship between the time dependent volume of pores in the matrix and the amount of drugs released from the implants.

INTRODUCTION

One modern way to get drug loaded implants is the polymerization technique (1-5). The resulting polymer matrix is comparable to the matrix of sustained release type tablets. An analysis of the release mechanism of such tablets was carried out in detail (6-9). But the polymerization technique brought matrix characteristics and release mechanisms different from that.

It has been shown that the fraction of drug release from the implants prepared by an extrusion polymerization technique of methacrylic ester (10) in the first time follows a first order mechanism (11) and in total it is linear with the square root of time (12). Furthermore it was obvious that the solubility and the particle size of the drug (11) and the geometry of the implant body (13) influence the drug release. These results and an investigation of the time dependent development of the volume of pores in the implants (14) have shown that the porosity may control the drug release rate as in the model described by Higuchi (9).

The aim of this work was to examine the effects that antibiotics and certain amino acids with different solubility have on the release properties of the implant matrix. In addition this paper also deals with a study of the mechanical strength of the matrix varying in dependence of the drying temperature.

MATERIALS AND METHODS

Chemicals

The drugs investigated were gentamicine (Pharmachim, Bulgaria) and streptomycine (VEB Jenapharm, DDR) as sulphates and chloramphenicol (VEB Berlin-Chemie, DDR).

Following pharmacopoe grades (15) excipients were used: glycine, valine, methionine, glutamine, cystine and titan dioxyde or amber acid respectively.
A methacrylic monomer (Kallocryl^{R} Af, VEB Spezialchemie, Leipzig, DDR) served as matrix forming material.

Preparation of implants

The drugs were mixed with the excipient and/or the powder component of Kallocryl^{R}. The mixture was extruded of a 2 mm diameter cord and polymerized simultaneous. After the drying process (12 h at 50 °C ± 1 K) the cord was cut in 10 mm pieces.

Mechanical strength

The bending strength was determined using the Erweka apparatus TBT (Erweka Apparatebau, Heusenstamm, FRG) as the force required to crack an implant between two edges in a distance of 11 mm.

Solubility

An amount of the sieved drug or excipient (particle size <315 mm) about 10 % higher than the expected solubility (Table 1,2) was dissolved in 100 ml buffer solution by Butz (pH = 7.4). The solution was mechanical moved (magnetic stirrer, 1 cm whirlpool). The solubility was calculated as described by equation 3(16) as point of intersection of the solubility line (eq. 1) with an auxiliary straight line ($c_2 = c_1$).

$$c_2 = k_1 c_1 + 1 \qquad \text{(Eq.1)}$$

c_1 = concentration at time t_1 (mg ml^{-1})

c_2 = concentration at time t_2 (mg ml^{-1})

$k_1, 1$ = constants

t_1, t_2 = time interval for sample removing

$$c_s = \frac{1}{1 - k} \quad (\text{mg ml}^{-1}) \qquad \text{(Eq.2)}$$

Drug release

To follow the release of the drugs a pitcher / half change method and conditions were used as described earlier (14). The liberation velocity coefficients (k_L) were calculated as the slope of equation 3.

$$\ln(100-c_t) = k_L\, t + a \qquad \text{(Eq.3)}$$

c_t = amount liberated (%) at time t (min)

RESULTS AND DISCUSSION

The initial drug release of antibiotics of different solubilities followed in good correlation the first order mechanism as described in equation 3. The velocity of drug release increased with the drug solubility as espected (Table 1).

TABLE 1

Velocity constants (k_L) of release of drugs with different solubility (c_s,)1 according to (15),)2 experimental) from implants with titan dioxyde or without excipients ()3) and correlation coefficients (r) following eq. 3 ($r' = 0.83$, $P = 0.99$, $f = 6$)

drug	c_s (mg ml^{-1})	particle size (µm)	k_L (10^3 min^{-1})	r
gentamicine	1000-3000)1	<130	- 0.141	0.934
streptomycine	1000- 100)1	<130	- 0.114	0.945
chloramphenicol		<130	- 0.032	0.999
chloramphenicol		130-250	- 0.009	0.976
chloramphenicol)3	5.5)2	<315	- 0.021	0.952

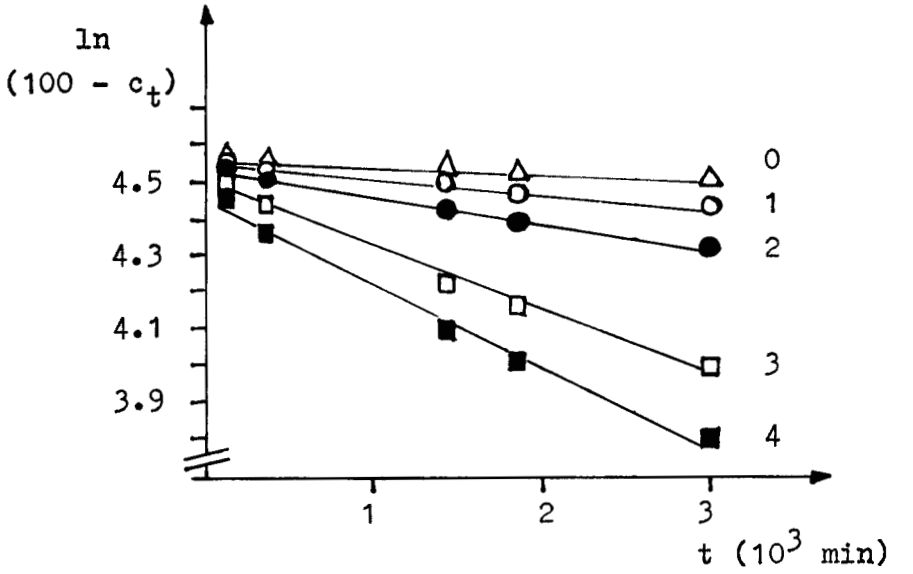

FIGURE 1

Amount of chloramphenicol released (c_t) at time (t) from implants without excipients (0), with cystine(1), glutamine (2), methionine (3) or valine (4).

The influence of the particle size of the drugs indicated a different trend. The chloramphenicol release decreased with increasing particle size. In the case of implants without an additional excipient the release of the drug was higher as expected.

The addition of amino acids as pore forming excipients was followed by an increasing chloramphenicol release (Fig.1). There was a linear relationship between the velocity constant and the solubility of the amino acids as followes:

$$k_L = 0.003\ c_s + 0.037 \qquad \text{(Eq.4)}$$

$$r = 0.997$$

$$r' = 0.998\ (P = 0.99,\ f = 2)$$

TABLE 2

Solubility of amino acids (c_s,)1 from literature (17))2 experimental) and resulting release velocity (k_L) of chloramphenicol from implants

amino acid	c_s (mg ml^{-1}))1	)2	k_L (10^{3} min^{-1})
glycine	250	270	- 0.130
valine	88.5	55.4	- 0.229
methionine	33.5	43.1	- 0.172
glutamine	32.4	11.8	- 0.074
cystine	0.1	0.3	- 0.041

The slightly soluble glycine makes an exception.(Tab. 2). That may be caused by a concurrence of drug and excipient release and the water inflow into the matrix. It is well known that the mechanical strength of a matrix influences the drug release (18). Knowing that the mechanical strength of the implants could be dependent upon the content of rest monomer in the matrix this content was reduced by modification of the drying temperature as discussed by (19).

The increasing drying temperature involved an increasing mechanical strength and a decreasing release velocity (Tab.3).

The release process from the implants includes a flow of water into the matrix and a flow of solute away from it. The first of these may be rate limiting dependent on the water solubility of the drug or excipient, and may determine the effect of concentration and particle size on release rate.

TABLE 3

Mechanical strength (F) , relevant standard deviation (s) and release velocity (k_L) of chloramphenicol from implants with glycine produced by different drying temperatures (T)

T (^oC)	10	40	70	100
F (N)	10.4	11.6	16.0	20.2
s (N)	0.9	0.5	1.2	1.9
k_L (10^3 min^{-1})	- 0.091	- 0.068	- 0.041	- 0.028

A previous investigation of the time dependent development of pores (14) suggest that the mentioned mechanism comes true to the studied implants. The water flow dependent volume of pores (V_p , ml) was found to be related to time (t, min) as followes:

$$\ln V_p = i + g \ln t \qquad \text{(Eq.4)}$$

$i = 0.481, \quad g = 0.453, \quad r = 0.987$

$r' = 0.96$ ($P = 0.99, \quad f = 3$)

Furthermore there was a linear relationship between V_p and the particle area (A, cm^2) of the excipient used in the mentioned investigation (amber acid):

$$V_p = h + k_2 A \qquad \text{(Eq.5)}$$

$h = 23.0, \quad k_2 = 0.03, \quad r = 0.999$

$r' = 0.96$ ($P = 0.99, \quad f = 3$)

In this way the drug release from the implants can be estimated from the physico-chemical parameters of the drugs and/or excipients and the connection of different parameters can provide usefull informations for the design of a delivery system for long term implantation in the bone.

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