Study of Additive Effect on Mechanical Properties, Drug Release Behaviour and Mechanisms in a Monolithic System

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ABSTRACT

In a monolithic controlled drug release system, the effect of drug and additives on release behaviour and mechanical properties of silicone elastomer were investigated. For this purpose the silicone matrixes containing different concentrations of progesterone, calcium carbonate and silicone oil as additives were prepared by mixing in thermo-mixer Haake and cured in specific conditions. Then the released drug was evaluated by a new analytical method and the mechanical properties were studied according to ASTM D 2240. The results indicate that the release profile that has been found by experimental data is in good agreement with Higuchi's model. When silicone oil and progesterone concentration were increased in polymer matrix, the drug release was increased but the hardness was decreased. The drug release was decreased by addition of calcium carbonate but this additive had no effect on hardness.

INTRODUCTION

Diffusion of drug through silicone elastomeric matrix as a controlled drug release system has recently been evaluated and good predictability has been achieved by assuming that the drug solute diffuses according to Fick's law. There have been many excellent papers on diffusion in one- and two-layer systems including one layer with dispersed phases [1-4].

Controlled release dosage forms can be classified on the basis of their release mechanism. Various mechanisms can be used to control drug

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release. Diffusion, swelling and degradation/erosion are the most important ones. Diffusion-controlled systems are divided into monolithic and reservoir systems. In monolithic (matrix) systems, the drug molecules that are dispersed homogeneously in the polymer matrix are released by permeation from its interior to the surrounding medium [5-9].

Developing a matrix system with a constant release rate has always been a challenge to pharmaceutical scientists. According to Fick’s first law of diffusion, the release of drug from monolithic matrix is inherently non-linear due to the increase in diffusional length resistance and/or the decrease in the inwardly releasing surface area with time [10]. Over the years, many research groups have studied drug release kinetics from various polymers and the effect of different factors on release profile [11-15].

The objectives of this research were: (1) to study the release mechanism of progesterone from a silicone elastomer as matrix system, (2) to investigate the initial loading effect, (3) to study the solubility and diffusivity of progesterone in the silicone matrix, (4) to investigate the effects of calcium carbonate and silicone oil on release profile, (5) application of a new method for release evaluation, and (6) to investigate the filler effects on the hardness of silicone matrix.

EXPERIMENTAL

Materials
The following materials were used in the study: Elastosil 3003/40 (Wacker Company, Germany); micronized progesterone (XIANJU Pharmaceutical Factory). All other chemicals and reagents were either medical or HPLC grades and used as received.

Preparation Method
The samples containing 5 (SM 1), 10 (SM 2) and 15 % (SM 3) (w/w) of micronized progesterone were fabricated by mixing of two-component silicone and drug in thermo-mixer Haake (system 90, Haake USA) for 1 h. The discs with 10 mm diameter and 2 mm thickness were cured by using compression moulding at 150 bar of pressure at 115 °C for 15 min. Discs characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Samples code</th>
<th>Amount of drug loading (mg)</th>
<th>Hardness (Shore A)</th>
<th>Amount of drug release (mg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM1</td>
<td>9.6</td>
<td>48</td>
<td>0.91</td>
</tr>
<tr>
<td>SM2</td>
<td>19.2</td>
<td>49</td>
<td>1.13</td>
</tr>
<tr>
<td>SM3</td>
<td>29.2</td>
<td>51.1</td>
<td>1.88</td>
</tr>
</tbody>
</table>

(a) Initial time of partition-controlled process.

10 % (w/w) micronized progesterone were prepared then silicone oil and calcium carbonate of 5, 10 (SM 4 and SM 5, respectively), 15 % (w/w) were added according to procedure mentioned above and then the drug release and mechanical properties were evaluated.

Study of Progesterone Release
Release of progesterone from silicone based discs was measured in a hydrodynamically well-characterized Chien permeation system at 37 °C. Ethanol/water (60%v/v) dissolution was prepared and heated to 37 °C before testing as release medium. For determination of progesterone release profile, each disc was mounted onto the orifice of each half cells of Chien permeation system. Each of the half cells was filled with 3 mL of above mentioned release solution. At different intervals from 1 h to 92 h release medium was completely withdrawn and immediately refilled with fresh solution.

Analytical Method
Progesterone determination in the release medium was performed by newly developed high performance thin layer chromatography (HPTLC) method. Chromatography was performed on 10 × 20 cm silica gel 60F254 HPTLC plates (Art. 5642, Merck). Standards and samples were applied to the plates by means of a TLC Sampler III automated spray-on instrument (Camag, Muttenz, Switzerland). The band length: 2 mm; distance between bands: 4 mm; distance from plate edges: 20 mm, and distance from plate bottom: 10 mm. Plates were developed in a twin-trough TLC chamber to 60 mm with toluene/2-propanol (10:1 v/v), without saturation. After development the plates were air-dried and the sample and standard zones were quantified by linear scanning at the maximum absorption wavelength.
of 252 nm (Figure 1), using Camag TLC Scanner III with deuterium source. Base-line separation is shown in the Figure 2. The regression equation was:
\[ y = 1.1457x + 24.518 \]
where, \( y \) is peak height and \( x \) is the amount of progesterone in nanogram, and the correlation factor was 0.999 for 27-145 nanogram/zone. The method has shown good recovery (99.8-100.9%) for various levels of spiked samples in the linear working range interval.

The relative standard deviation of repetitive measurements (n=7) was 0.08-0.39 nanogram/zone, and limit of quantification was 5 gram/zone. The analytical weights in the sample zones were determined from their peak heights by interpolation from the regression curve.

RESULTS AND DISCUSSION

According to Higuchi equations the release pattern of drug from a drug-dispersed polymer matrix can be defined by the two following equations[16]:
\[
\delta_m^2 + 2 \frac{(A - C_p)D_p \delta_d \delta_m}{(A - C_p / 2)D_s kk} = \frac{2C_p D_p}{(A - C_p / 2)} t
\]
\[ Q = A \delta m \]  
(2)

Where, \( Q \) is the cumulated amount of drug release from a unit surface area (mg/cm²), \( A \) is the initial amount of drug impregnated in a unit volume of polymer matrix (mg/mL), \( C_p \) is the solubility of drug in the polymer phase (mg/mL), \( \delta_d \) and \( \delta_m \) are the thicknesses (cm) of

So, eqn (1) is reduced to:
\[
\delta_m^2 << 2 \frac{(A - C_p)D_p \delta_d \delta_m}{(A - C_p / 2)D_s kk}
\]

Substituting eqn (4) for the \( \delta_m \) term in eqn (2) gives:
\[
Q = \frac{-kD_s kC_p}{\delta_d} t
\]

Since the experiments were so designed that the initial amount of drug (A) incorporated into a unit volume of polymer matrix is much greater than the solubility (\( C_p \))
of the drug in this polymer, therefore \((A-C_p) = A\).

We know that \(C_s = kC_p\), so, eqn (5) may be transformed to:

\[
Q = \frac{kD_tC_s}{\delta_d} t
\]  

Eqn (6) indicates that at a very early stage of drug release dynamics, the partition-controlled process at the hydrodynamic diffusion layer is the rate-limiting step \((Q \propto t)\). After the lapse of a finite time, the thickness of the drug depletion zone, \(\delta_m\), becomes substantially greater, and it is impossible to consider \(\delta_m\) of eqn (3) negligible. So, it is reduced to:

\[
\delta_m = \left[\frac{2C_pD_p}{(A-C_p/2)}\right]^{1/2}
\]  

Substituting eqn 7 for the \(\delta_m\) term in eqn (2) and considering \((A-C_p/2) = A\), eqn (8) is obtained:

\[
Q = \left[2AD_p C_p\right]^{1/2} t^{1/2}
\]  

Eqn 8 indicates that after a finite period of drug elution, a matrix-controlled process becomes the predominant step in determining the mechanism of drug release from the polymer matrix \((Q \propto t^{1/2})\).

In this research work the release of progesterone from a silicone polymer matrix containing 10 % (SM2) drug is evaluated and the early stage of drug release \((\leq 3 \text{ h})\) is illustrated in Figure 4. Theoretical analyses conducted earlier suggested that this initial state drug release is predominantly a partition-controlled process in the hydrodynamic diffusion layer (Figure 3) and a zero order drug release profile should be observed.

The thickness of the drug depletion zone, \(\delta_m\) (Figure 3) has proceeded with time. In this case, the matrix-controlled process is a predominant process. Therefore, the cumulative amount of drug release from a unit surface area of the polymeric matrix should become proportional to the square root of time. The results are shown in Figure 5 confirming this linear relationship. Also, the initial loading dose effect was studied (Figure 6). According to eqn (2), cumulative release is increased with increasing loading dose of progesterone in matrix. But eqn (7) indicates that \(\delta_m\) is proportional to \(A^{-1/2}\). It means that in the specific time,

\[
\delta_m = \left[\frac{2C_pD_p}{(A-C_p/2)}\right]^{1/2}
\]
δ_m is exponentially decreased with increasing initial loading dose. Therefore, the varieties of Q for samples containing 10-15% drug are lower than 5-10% drug. But it should be emphasized that Q will be increased due to increasing A.

According to eqn (8), the drug release-flux (Q/t^{1/2}) depends linearly on (2A)^{1/2}, which is a characteristic of matrix-type drug delivery systems (Figure 7).

As shown in Figure 8 the addition of calcium carbonate as an inert filler reduces the diffusivity by increasing tortuosity of the diffusion path and increases the diffusional distance. Then the drug molecules must migrate through longer distances in order to reach the silicone surface and to be released to the medium.

Also calcium carbonate is known as an inactive fillers with semi-reinforcing property and it does not show considerable effects on hardness (Table 2).

According to Figure 8 the drug release was increased by addition of silicone oil, because it increased the diffusivity of drug through matrix and decreased the hardness of polymer by increasing the chain mobility as a plasticizer (Table 2).

**CONCLUSION**

In summary, the in vitro controlled release of progesterone from a drug-dispersed silicone polymer containing 5, 10, 15% (w/w) of drug was investigated. The release behaviour of drug into the medium was evaluated in Chien permeation system. Progesterone content of release medium was determined by a newly developed high performance thin layer chromatography method. The method has shown good recovery for various levels of spiked samples. The results have indicated that drug release from the discs in the initial state was predominantly a partition-controlled process and after the drug diffusing out it was mainly a matrix-controlled process. There is an increase in cumulative amount of drug release with increasing initial loading dose based on Higuchi equations. There is a different effect of fillers upon the release of drug from silicone matrix. The addition of silicone oil to the silicone elastomer decreases the hardness of polymer and increases the release rate of progesterone, and calcium carbonate, with no effect on hardness, decreases the in vitro release rate of drug.

**REFERENCES**

4. Chandrasekaran S.K. and Paul D.R., Dissolution-con-


