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Controlled Release of Progesterone from Polyethylene Oxide-Silicone Rubber Matrix

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Abstract□The release of progesterone from monolithic devices composed of different ratios of polyethylene oxide (PEO; mw 20,000) and hydrophobic polydimethylsiloxane was investigated. Water soluble PEO soaked into the polymer provided controlled release of progesterone. The release rate of progesterone could be controlled by varying the contents of PEO and progesterone in soaking solution. The progesterone release rate from silicone devices increased as the content of PEO in devices increased, while it decreased as the content of PEO in soaking solution increased. The release rate may be made by simple alterations of geometry of devices controlled swelling and the change in the physical structure of polymer network. Hydrophobic polydimethylsiloxane containing PEO and progesterone can provide a contraceptive material for prolonged release of progesterone.

Keywords□progesterone release, silicone rubber, polyethylene oxide, drug delivery system.

Polydimethylsiloxanes (silicone rubber) have long been used for biomedical application such as catheters, artificial hearts and heart assist pump[1]. The advantage of silicone rubber for long term drug delivery systems have been recognized[2].

In 1966, the steroids placed in silicone rubber tubes, released into a solution of saline at constant rate for several days, was first reported by Dziuk *et al.*[3] Sundram *et al.* have reported that steroids hormones could be diffused through silicone rubber, and especially progesterone and silicone rubber implanted in cattle would release the drug for more than one year and could be used to controlled fertility[4]. Ho *et al.* have reported that simulation studies with progesterone and hydrocortisone illustrate matrix releaselimiting, membrane absorption, and aqueous diffusion layerlimiting cases when the cylindrical silicone delivery device is interfaced with the vaginal membrane of rabbits[5]. Roseman studied the amounts of drug released from silicone rubber matrix. systems depend upon the molecular structure of the steroids[6]. Roseman *et al.* reported that a model system was presented for the release of a water-insoluble steroid, medrosyprogesterone acetate, embedded in solid silicone rubber[7].

Colter *et al.* determined the effectiveness of thin plasma-polymerization films for controlling the flux of progesterone through silicone rubber membrane[8]. For the preparation of the progesterone blended polymers that release the drug by diffusion, effective dose level of released progesterone should be considered. In order to control the release rate of hydrophobic drugs through hydrophobic polymers, water soluble carrier functioning as swelling agents such as polyethylene oxide (PEO) can be utilized.

The purpose of this work was to examine the progesterone release from silicone rubber as a function of PEO content for the effective release rate and optimization of long term release of progesterone.

Rationale for the selection of PEO is that PEO is a water soluble hydrophilic polymer. It is our hypothesis that PEO, aside from increasing the water content of the hydrophobic matrices, will slowly diffuse with progesterone to the matrix surface. Thus, PEO has a dual role of increasing hydration of matrix and capping progesterone in the water-filled channels.

EXPERIMENTAL METHODS

Materials

Polydimethylsiloxane (382 Medical grade Silastic Elastomer, Dow Corning), stannous octoate (Dow Corning), polyethylene oxide (mw 20,000, Sigma Chemical Company), progesterone (Sigma Chemical Company), and chloroform (Fisher Chemical Company) were used as received.

Methods

Cylindrical monolithic matrices of both the PEO/silicone rubber and silicone rubber were prepared by vulcanization on a polyethylene mold. PEO was dissolved in 3 ml of chloroform, and added to the silicone rubber and stirred to obtain a homogeneous dispersion. After evaporation of the chloroform, stannous octoate was then added into the sample to catalyze the vulcanization process.

Both the PEO/silicone rubber blend and silicone rubber were applied onto polyethylene mold and then degassed under high vacuum (20 μm Hg). After vulcanzation at room temperature for 24 hours, the cylindrical matrices were removed from the polyethylene mold and vacuum dried at room temperature for 24 hours. Cylindrical devices were cut having dimensions of 1.00 cm in height and 0.575 cm in radius.

Before loading the PEO and progesterone, all the matrices containg PEO were soaked to remove PEO in the 30 ml chloroform for 3 days. The devices were allowd to day under high vacuum (20 μm Hg) at room temperature for 24 hours.

In order to load PEO and progesterone, all the devices were soaked in 2 ml of progesterone/PEO/chloroform solution at room temperature (24 ± 1 °C) for 24 hours. The devices were allowed to dry under high vacuum (20 μm Hg) at room temperature for 24 hours.

All devices were washed twice with deionized water to remove surface contaminants. For the drug release experiments the progesterone/PEO/silicone rubber devices were immersed into 20 ml of deionized water at room temperature (24 ± 1 °C). To minimize boundary layer effect, the releasing media were stirred continuously by constant speed magnetic stirrer. The releasing media were withdrawn at time intervals and replaced with fresh deionized water.

The concentration of released progesterone was assayed by spectrophotometry at 248nm. The experiments were performed in duplicate and the mean results were reported.

RESULTS

Polymer matrices of silicone rubbers soaked in a fixed progesterone content (5 w/v %) and different PEO contents were prepared. The PEO dependent

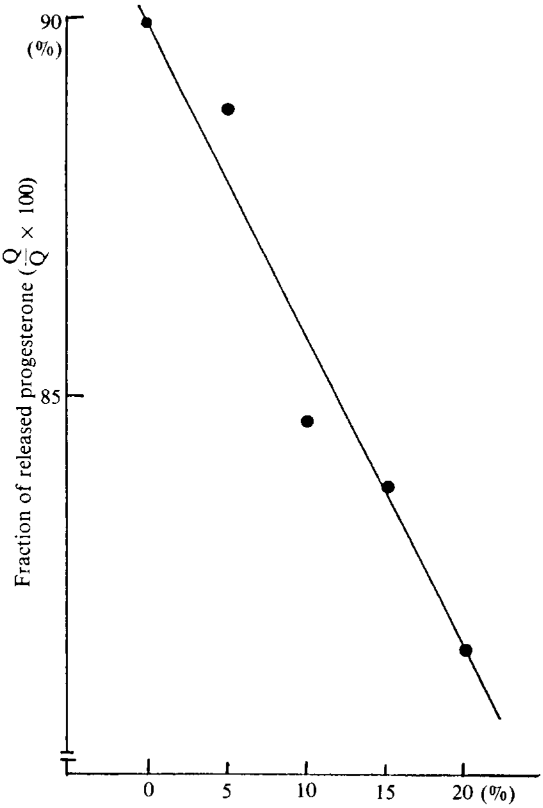
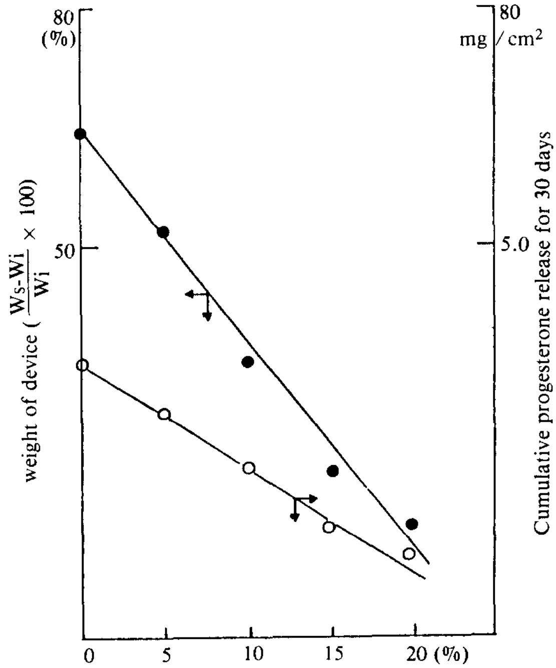


Fig. 1. The fraction of released progesterone versus loading dose of PEO 20,000 in the 5 w/v% progesterone/silicone rubber devices for 100 days.

release rate of progesterone from these cylindrical monolithic matrices are shown in Fig. 1. The release of progesterone from the matrices in the absence of PEO was high. As the PEO content in the matrices increased, significant decrease in progesterone release resulted. The release rates decreased with increased PEO loadings. As shown in Fig. 2, the increase of weight from matrices in a absence of PEO in soaking solution was high. As the PEO content in soaking solution increased, significant decrease in amount of progesterone released and increase in weight of matrices resulted. The release rates and weight change decreased with increased PEO content in soaking solution.

Table I shows the cumulative of amount of progesterone released for 30 days from the polymer matrices soaked in solution containing 20 w/v % progesterone and different w/v % PEO. Table II shows the equilibrium water content and amount of progesterone released into deionized water for 30 days. After removal of the contained PEO by chlo-



* Ws: after soaking weight of devices
* Wi: Before soaking weight of devices

Fig. 2. Weight increase and cumalative progesterone release of silicone rubber matrices after soaking on the different concentration of PEO and 5 w/v% progesterone solution.

Table I. Progesterone release from silicone matrices with different PEO contents.

w/v % PEO in chloroform	Cumulate[a] amount released (mg/cm²)	Release rate (μg/cm²/day)
5	2.237	74.552
10	2.192	73.069
20	2.135	71.163
30	1.898	63.262

a) Cumulative amount of released progesterone per initial surface area.
All devices were soaked in PEO-progesterone/chloroform solution for 24 hrs.
All devices were released for 30 days.
progesterone was loaded from 20% solution.

roform the silicone devices were loaded with progesterone in 20 w/v % progesterone solution. The progesterone release rate increased upto at 15% PEO content, then decreased at 20% PEO content. However, the release rate simply decreased as the PEO content increased when the release experi-

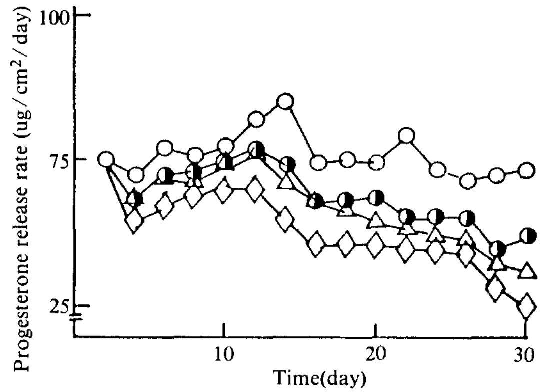


Fig. 3. Release rate of progesterone released from silicone rubber devices which were soaked in defferent PEO and 20 w/v % progesterone in $CHCL_3$.
○-○ 5 w/v % PEO ◐-◐ 10 w/v % PEO
△-△ 20 w/v % PEO ◇-◇ 30 w/v % PEO

Table II. Equilibrium water contents and progesterone release from silicone matrices with different PEO contents.

w/v % PEO loading dose	Wf[b]	Cumulative amount released (mg/cm²)	Release rate (μg/cm²/day)
0	—	2.026	67.530
1	0.597	2.170	72.336
5	8.367	2.309	76.963
10	23.000	2.385	79.488
15	33.940	2.521	84.018
20	49.870	2.316	77.208

All devices were released for 30 days.
Progesterone was loaded from 20% solution.
b) Water fraction = $\frac{\text{Wet weight-dry weight}}{\text{Dry weight}} \times 100$

Table III. Equilibrium water contents and progesterone release from silicone matrices with different PEO contents.

w/v % PEO in chloroform	Wf	Cumulative amount released (mg/cm²)	Release rate (μg/cm²/day)
5	78.830	4.699	52.208
10	88.570	3.887	43.190
20	100.000	3.848	42.753
30	91.740	3.421	38.012

All devices were released for 90 days.
Progesterone was loaded from 20% solution.

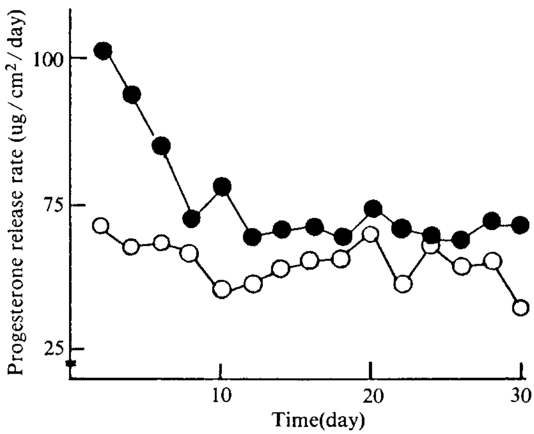


Fig. 4. Release rate of progesterone released from silicone rubber devices with defferent PEO loading which were soaked in 20 w/v % progesterone in $CHCL_3$.

○-○ 0 w/w % PEO ●-● 20 w/w % PEO

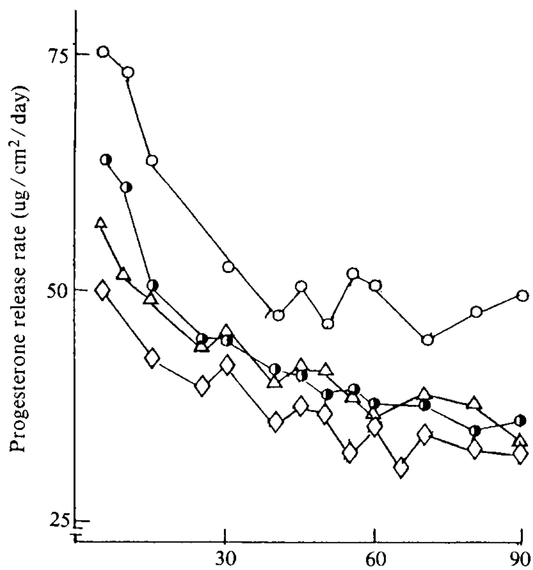


Fig. 5. Release rate of progesterone released from silicone rubber devices with 20 w/w % PEO loading which were soaked in different PEO and 20 w/v % progesterone in $CHCL_3$.

○-○ 5 w/v % PEO ◑-◑ 10 w/v % PEO

△-△ 20 w/v % PEO ◇-◇ 30 w/v % PEO

ments were performed upto 90 days (see Table III). The release rates for these matrices are shown Figs. 3,4 and 5.

All the matrices had similar release profiles. These are intial burst effect followed by rapid decline of release rate (see Figs. 3, 4, and 5).

DISCUSSION

In the previous work[9], the release rates of progesterone from progesterone/silicone rubber matrices as an intrauterine device were not sufficient to prevent fertility. A typical release profile showed an initial burst effect followed by a rapid decline of progesterone release rate. The release rate of progesterone from most of the matrices maintained a constant release rate of 60 ug/day upto 30 days (see Tables I and II and Figs. 3 and 4). The elease rate dropped below 60 ug/day after 30 days of release (see Table III and Fig. 5).

It is considered that progesterone close to the polymer-solvent interface is released during the initial burst effect period. Then hydrophobic silicone rubber regulates the progesterone within the matrices by dissolving and diffusing from the matrices (see Table II). Thus, the progesterone release rate was sufficient to maintain contraceptive level established by Baker *et al.*[10]. During the soaking process in progesterone/PEO solution, the minimal concentration of PEO in soaking solution enhanced absorption of progesterone within the hydrophobic silicone rubber matrices.

PEO, blended with the hydrophobic matrices, is used to increase the water content. The higher water content would allow dissolution of the progesterone within the matrices. Also, the hydration of matrices probably creates pores, though which progesterone diffuses.

According to Graham *et al.*[11] and polson[12], interactions between PEO and water increases as PEO concentration increases. These interactions result in structual changes of PEO to random coil formation. On the other hand, Sun *et al.*[13] and Liu *et al.*[14] reported that the presence of polar compounds in the silicone rubber reduced the rate of permeation of testosterone and mass transfer properties were varied by changing the viscosity and the density of the dissolution medium. The progesterone dispersed in PEO may have an ability to diffuse into random coil structure of PEO in aqueous solution.

These results show a relationship between the release rate of progesterone and content of PEO. PEO was found to be a good agent to control progesterone release from slicone rubber devices because the release characteristics were related to the water content of polymer.

For silicone rubber matrices without PEO, the progesterone release rate decreased with PEO soaking. In contrast, the release rate of silicone rubber matrices, PEO loading, increased with PEO soaking.

CONCLUSION

Polyethylene oxide proved to be an active agent to extend progesterone release from progesterone containing silicone rubber matrices. The release characteristics of progesterone were dependent on the PEO content. The mechanism governing progesterone release will be studied further by *in vivo* experiments.

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