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Influence of silicone elastomer solubility and diffusivity on the in vitro release of drugs from intravaginal rings

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Abstract

The in vitro release characteristics of eight low-molecular-weight drugs (clindamycin, 17β-estradiol, 17β-estradiol-3-acetate, 17β-estradiol diacetate, metronidazole, norethisterone, norethisterone acetate and oxybutynin) from silicone matrix-type intravaginal rings of various drug loadings have been evaluated under sink conditions. Through modelling of the release data using the Higuchi equation, and determination of the silicone solubility of the drugs, the apparent silicone elastomer diffusion coefficients of the drugs have been calculated. Furthermore, in an attempt to develop a quantitative model for predicting release rates of new drug substances from these vaginal ring devices, it has been observed that linear relationships exist between the log of the silicone solubility of the drug (mg ml⁻¹) and the reciprocal of its melting point (K⁻¹) (y = 3.558x – 9.620, R = 0.77), and also between the log of the diffusion coefficient (cm² s⁻¹) and the molecular weight of the drug molecule (g mol⁻¹) (y = -0.0068x – 4.0738, R = 0.95). Given that the silicone solubility and silicone diffusion coefficient are the major parameters influencing the permeation of drugs through silicone elastomers, it is now possible to predict through use of the appropriate mathematical equations both matrix-type and reservoir-type intravaginal ring release rates simply from a knowledge of drug melting temperature and molecular weight.

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Keywords: Silicone; Intravaginal ring; Drug delivery; Diffusion coefficient; Solubility

1. Introduction

Intravaginal rings (IVRs) are elastomeric drug delivery devices specifically designed to provide controlled and sustained release of substances to the vagina of the human female for either local or systemic effect (Fig. 1) [1–4]. Since the IVR concept was first established in 1970 [5–7], most of the research has focused on the development of steroid-releasing rings, for either contraceptive [1–9] or hormone replacement therapies [10–14]. As a result,
steroids which permits relatively rapid molecular diffusion. Specifically, drug release has been shown to depend primarily on the silicone elastomer diffusivity \( (D_{\text{SIL}}) \) and the silicone elastomer solubility \( (C_{\text{SIL}}) \) of the drug molecule, as described by cumulative release Eqs. (1) and (2) for matrix and reservoir-type devices, respectively [10,16,18–20]

\[
Q = \sqrt{D_{\text{SIL}}(2A - C_{\text{SIL}})C_{\text{SIL}}t}
\]

\[
Q = \frac{D_{\text{SIL}}C_{\text{SIL}}}{h_{\text{sheath}}}, t
\]

where \( Q \) is the cumulative amount of drug released per unit area of device \( (\text{mg cm}^{-2}) \), \( A \) is the drug loading \( (\text{mg cm}^{-2}) \), \( C_{\text{SIL}} \) is the solubility of the drug in silicone elastomer \( (\text{mg cm}^{-2}) \), \( D_{\text{SIL}} \) is the diffusivity of the drug in the elastomer \( (\text{cm}^2 \text{ day}^{-1}) \), \( h_{\text{sheath}} \) is the thickness of the sheath layer \( (\text{cm}) \) and \( t \) is the time \( (\text{days}) \). However, the IVR platform might also be effectively employed to deliver nonsteroidal molecules, having the requisite physicochemical characteristics, for a range of other therapies within women’s healthcare. Yet, to date, the only nonsteroidal drugs evaluated for IVR administration are oxybutynin for the treatment of urinary incontinence [21,22], nonoxynol-9 as a potential anti-HIV vaginal microbicide [23], and bromocryptine mesylate for the treatment of hyperprolactinaemia [24]. The preconception still persists that silicone IVRs are only suitable for the administration of steroidal molecules for contraceptive and hormone replacement therapies.

Although a significant body of work has been published to date on the development, application and clinical testing of IVRs, no attempt has yet been made to develop a model for predicting drug release rates. In fact, only a small number of publications have been reported in the scientific literature which focus on the major parameters influencing IVR release rates, namely polymer solubility and diffusivity [10,14,16,18,19,25]. Such a model would be a particularly useful tool in evaluating the potential for new drug substances to be effectively released from a silicone IVR device. Necessarily, any predictive model should be based on real IVR release data, and is likely to be based on certain physicochemical properties of the drug substances themselves. In order to elucidate the relative importance of these

three steroidal IVR products have now reached the market: Estring\textsuperscript{®} (17\( \beta \)-estradiol; Pharmacia and Upjohn), Menoring\textsuperscript{®} (17\( \beta \)-estradiol-3-acetate; Galen Holdings), and Nuvaring\textsuperscript{®} (etonogestrel and ethinyl estradiol; Organon). Much of the IVR literature relates to crosslinked poly(dimethylsiloxane), or silicone devices, although other elastomeric polymers have been employed in recent years e.g. poly(ethylene–co-vinyl acetate) and styrene–butadiene block copolymers [15–17]. Silicone, in particular, lends itself well to the release of steroid molecules, a consequence of the relatively high solubility of steroids in the hydrophobic silicone and the relatively low molecular weight/volume of the

Fig. 1. (A) Silicone intravaginal ring; (B) X-ray image showing position of silicone intravaginal ring positioned in the human female.
physicochemical parameters, the solid drugs of this study were selected to represent permeants having a range of molecular size and hydrophilic/lipophilic characteristics. In this study, the solubility and diffusivity factors influencing the controlled release of a range of steroidal and nonsteroidal molecules from silicone IVRs have been determined, and a model has been developed that will allow qualitative assessment of the potential to release new drug substances from silicone IVR devices.

2. Materials and methods

2.1. Materials

17β-Estradiol (E2) was obtained from Schering Health (West Sussex, UK). 17β-Estradiol-3-acetate (E3A) was synthesized under GMP conditions by Irotech (Cork, Ireland). Metronidazole (MET) was supplied by Mediolast Spa (Milan, Italy). Norethisterone (NET) and norethisterone acetate (NETAc) were supplied by Galen Holdings (Larne, Northern Ireland, UK). Clindamycin (CLIN) was obtained from Lek (Ljubljana, Slovenia). Oxybutynin free-base was supplied by Orgamol (Evionnaz, Switzerland). HPLC grade tetrahydrofuran, ethyl acetate and GPR grade hexane were purchased from LabScan (Dublin, Ireland). Benzalkonium chloride (BKC, 50% aqueous solution), acetic anhydride and dimethylpolysiloxane (viscosity, 20 cSt) were purchased from Aldrich–Sigma (Poole, Dorset, UK). MED-6382 silicone elastomer base and tetrapropoxysilane crosslinker were supplied by Nusil Technology (Carpinteria, CA, USA). Stannous octoate was obtained from Air Products and Chemicals (Pennsylvania, PA, USA).

2.2. Synthesis of estradiol-3,17-diacetate

Freshly distilled acetic anhydride (4.95 g, 0.048 mol) and anhydrous zinc chloride (0.03 g, 0.0002 mol) were added to a solution of E3A (15.02 g, 0.048 mol) in 120 ml of sodium-dried and distilled tetrahydrofuran. The solution was refluxed for 5 h before removing the solvent to yield a crude white powder. Purification by column chromatography (silica gel, eluent. ethyl acetate–hexane, 25:75) yielded 16.04 g of estradiol-3,17-diacetate (94% yield, m.p. 120–121 °C). The chemical structure was confirmed by 13C-NMR, FT-IR and HPLC. 13C-NMR: C=O signals, 169.38 and 170.36 ppm (cf. E3A, 169.40 ppm); FT-IR: C=O peaks, 1733.9 and 1766.5 cm⁻¹ (cf. E3A, 1734.0 ppm).

2.3. High-performance liquid chromatographic analysis

HPLC assays were developed to quantify in vitro drug release from the IVRs (Section 2.5) and to measure the solubility of the drugs in poly(dimethylsiloxane) fluid (Section 2.6). Details of the HPLC assays are summarized in Table 1 for each drug. The HPLC instrumentation (Shimadzu, Kyoto, Japan) consisted of a model SIL-10AXL autoinjector, a model SCL-10A system controller, a model LC-10AT solvent delivery module, a model FCV-10AL low-pressure gradient-flow valve, a model GT-154 degassing unit, and a model SPD-10A UV–Vis detector. Injection volumes were 10 μl.

2.4. Preparation of matrix-type intravaginal rings

Matrix rings containing various drug loadings (50, 125, 250, 500 and 1000 mg) of CLIN, E2, E3A, EDA, MET, NET, NETAc and OXY were manufactured by reaction injection moulding according to the following standard method. A standard silicone elastomer mix was prepared by mixing together 51.2 g tetrapropoxysilane and 2048.8 g MED 6382 silicone elastomer base. The base consisted of a mixture of high- and low-molecular-weight hydroxy-terminated silicones (Mₙ = 10 000 and 2000, respectively) and 25% (w/w) of the micronised reinforcing filler diatomaceous earth. The required amount of drug was added to and intimately mixed with 30.0 g of the silicone mix. Stannous octoate (0.5%, w/w) was then added, the elastomer mixture hand-mixed for 30 s with a spatula and then injected via a disposable 60-ml plastic syringe into the stainless steel moulds of a laboratory-scale, electrically-heated IVR reaction injection moulding machine specifically designed for the manufacture of intravaginal rings (Technigal Division of Galen Holdings, Craigavon,
Table 1
Details of HPLC assays for drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Column</th>
<th>Mobile phase</th>
<th>Flow-rate (ml/min)</th>
<th>Det.A (nm)</th>
<th>Retention (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLIN</td>
<td>Hypersil ODS BDS</td>
<td>CH$_3$CN–0.02 M buffer, pH 5–water (25:44:31)</td>
<td>1.0</td>
<td>210</td>
<td>5.29</td>
</tr>
<tr>
<td>E2</td>
<td>Sphereclone ODS2</td>
<td>CH$_3$CN–H$_2$O (50:50)</td>
<td>1.5</td>
<td>220</td>
<td>2.36</td>
</tr>
<tr>
<td>E3A</td>
<td>Hypersil ODS BDS</td>
<td>CH$_3$CN–H$_2$O (50:50)</td>
<td>1.5</td>
<td>220</td>
<td>5.84</td>
</tr>
<tr>
<td>EDA</td>
<td>Sphereclone ODS2</td>
<td>CH$_3$CN–H$_2$O (90:10)</td>
<td>1.0</td>
<td>220</td>
<td>2.96</td>
</tr>
<tr>
<td>MET</td>
<td>Hypersil ODS BDS</td>
<td>CH$_3$CN–0.02 M buffer, pH 5.0 (20:80)</td>
<td>1.0</td>
<td>277</td>
<td>2.13</td>
</tr>
<tr>
<td>NET</td>
<td>Sphereclone ODS2</td>
<td>CH$_3$CN–H$_2$O (50:50)</td>
<td>1.5</td>
<td>220</td>
<td>2.78</td>
</tr>
<tr>
<td>NETA</td>
<td>Sphereclone ODS2</td>
<td>CH$_3$CN–H$_2$O (50:50)</td>
<td>1.5</td>
<td>220</td>
<td>5.05</td>
</tr>
<tr>
<td>OXY</td>
<td>Luna ODS</td>
<td>CH$_3$CN–0.02 M buffer, pH 5.0 (45:55)</td>
<td>1.5</td>
<td>220</td>
<td>2.00</td>
</tr>
</tbody>
</table>

UK). The injection mixes were cured at 80°C for 2 min producing elastomeric silicone rings weighing 10.2±0.1 g and having the following dimensions: 7.5 mm cross-sectional diameter, 43.0 mm internal diameter, 58.0 mm external diameter. The surface area (using equation $s = 4 \pi^2 bc$ where $s$ is surface area, $b$ is the cross-sectional radius and $c$ is the external radius) and volumes (using $v = 2 \pi^2 b^2 c$) of the IVRs were calculated to be 37.4 and 7.01 cm$^3$, respectively.

2.5. Drug release studies

The steroid-containing rings were individually placed in stoppered 250-ml conical flasks containing 100 ml of a 1% (w/w) aqueous BKC solution. For CLIN, MET and OXY release experiments, 100 ml of 0.02 M phosphate buffer, pH 5.0, was employed. The release mediums were selected to maintain sink conditions over a 24-h release period. The flasks were shaken for 14 days in an orbital incubator (Sanyo Gallenkamp Model IOX400.XX2.C, 60 rpm, 37°C, 32 mm orbit diameter) with samples taken and release medium replaced fully every 24 h. Release studies were performed in triplicate.

2.6. Determination of drug solubility in silicone oil

Approximately 100 mg of each drug was added to 3.0 ml of 20 cSt poly(dimethylsiloxane) fluid. After equilibration for 72 h in a shaking orbital incubator at 37°C, the saturated silicone solutions were filtered at 37°C (Nalgene cellulose acetate filters, 0.2 μm) and 1.0 ml of the silicone filtrate was then extracted with 50 ml of the relevant mobile phase (Table 1). Drug solubilities in silicone ($C_{\text{sil}}$) were then determined using the HPLC assays already described for each drug substance (Section 2.3).

3. Results and discussion

The solid, micronised, pharmaceutical grade drugs employed in this study were incorporated into the silicone elastomer base at various loadings and cured at an elevated temperature produce IVRs containing a homogeneous dispersion of the drug within the matrix environment of the crosslinked silicone elastomer. The rings thus displayed typical matrix-type, diffusion-controlled release characteristics where mean daily drug release was proportional to drug concentration, as exemplified in Fig. 2 for norethi-
Fig. 2. Fourteen-day daily release profiles of norethisterone from matrix-type intravaginal rings of various drug loadings. ■, 50 mg; ◆, 125 mg; ▲, 250 mg; ○, 500 mg; *, 1000 mg.

terone-loaded IVRs. Similar matrix-type release profiles were obtained for the other drug-loaded IVRs. The release profiles are characterized by an initial burst followed by a gently decreasing daily release. The standard deviation for each mean daily release data point \( n = 3 \) is smaller than the height of the plot symbols (coefficient of variance <2%) and error bars have therefore been omitted. This high degree of reproducibility in in vitro studies is typical for IVRs produced in our laboratory, which are manufactured by reaction injection moulding on a laboratory-scale ring making machine using precision-engineered stainless steel moulds identical to those used in the commercial manufacturing process.

According to the Higuchi equation [Eq. (1)], diffusion-controlled release from matrix-type IVRs should produce linear \( Q \) versus \( t^{1/2} \) cumulative release profiles having a gradient equal to \( [D_{\text{StL}}C_{\text{StL}}(2A - C_{\text{StL}})]^{1/2} \), as exemplified for norethisterone IVRs in Fig. 3. IVRs loaded with the other drug substances displayed entirely similar profiles. The linear correlation coefficient, \( r^2 \), for the 14-day \( Q/t^{1/2} \) profiles was \( >0.995 \) for each IVR formulation except the 50 mg NETAc and 50 mg EDA rings where drug exhaustion of the matrix was evident beyond day 10. However, \( r^2 >0.997 \) over 10 day release profiles for these rings. The cumulative release flux rates (\( Q/t^{1/2} \)) for the 250- and 1000-mg drug-loaded rings are presented in Table 2 for each of the drugs investigated. The trend in increasing release rates was \( \text{CLIN}<\text{E2}<\text{NET}<\text{MET}<\text{E3A}<\text{NETAc}<\text{EDA}<\text{OXY} \). Entirely similar trends were observed for the other drug loadings.

Acetyling the 3-hydroxyl and 17-hydroxyl groups of E2 and NET, respectively, provided significantly faster release rates than the corresponding parent steroid. For E3A, the \( Q/t^{1/2} \) flux rate was some 7 times greater that for E2, while NETAc provided a 4.5-fold enhancement over NET. A further increase in the flux rate is observed for EDA. The trend in release amongst the structurally-similar steroids seems to relate to the number of hydroxyl groups within the steroids-E2, NET, E3A, NETAc and EDA have 2, 1, 1, 0 and 0 hydroxyl groups.

Table 2

Flux rates of drugs from 250- and 1000-mg loaded matrix-type intravaginal rings

<table>
<thead>
<tr>
<th>Drug</th>
<th>( Q/t^{1/2} ) (mg cm(^{-2}) t(^{-1/2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 mg IVR</td>
</tr>
<tr>
<td>CLIN</td>
<td>0.063</td>
</tr>
<tr>
<td>E2</td>
<td>0.120</td>
</tr>
<tr>
<td>E3A</td>
<td>0.847</td>
</tr>
<tr>
<td>EDA</td>
<td>1.117</td>
</tr>
<tr>
<td>MET</td>
<td>0.278</td>
</tr>
<tr>
<td>NET</td>
<td>0.252</td>
</tr>
<tr>
<td>NETAc</td>
<td>1.139</td>
</tr>
<tr>
<td>OXY</td>
<td>3.069</td>
</tr>
</tbody>
</table>
polar molecule in the hydrophobic silicone elastomer.

Values of $Q/t$, obtained by squaring the line gradients from the $Q$ versus $t^{1/2}$ plots (Fig. 3), were then plotted against $(2A - C_{sIL})$, producing a straight-line correlation of gradient $D_{sIL}C_{sIL}$ according to Eq. (1). The linear $Q/t$ versus $(2A - C_{sIL})$ plot for the NET rings is presented in Fig. 4. Matrix IVRs containing the other drug substances produced similar straight-line $Q/t$ versus $(2A - C_{sIL})$ plots ($r^2 > 0.993$), the gradient product $D_{sIL}C_{sIL}$ of which are presented in Table 3. The trend in increasing magnitude of the $D_{sIL}C_{sIL}$ values (CLIN < E2 < NET < MET < E3A < NETAc < EDA < OXY) reflects the trend observed for increasing release flux rates $Q/t^{1/2}$ (Table 2).

Having arrived at an experimentally derived value for the product of the diffusion coefficient and the solubility of the drug in silicone elastomer, a value for the diffusion coefficient may be easily calculated if the solubility of the drug in silicone can be measured. Several methods for determining the silicone solubility of compounds have been reported in the literature, including (i) the use of a low-molecular-weight/low-viscosity silicone oil as a surrogate for silicone elastomer [10,18,19,26,27], (ii) differential scanning calorimetry [28], (iii) dynamic mechanical analysis [19], and (iv) diffusion of drug from a saturated drug solution into a thin film of silicone elastomer [16]. The silicone oil method was adopted in this study owing to its simplicity. The solubility of each drug in silicone oil at 37 °C ($C_{sIL}$) is presented in Table 3. The trend in increasing solubility is E2 > MET > CLIN > NET > E3A > NETAc > EDA > OXY. It is apparent that the difference

![Graph](https://via.placeholder.com/150)

Fig. 4. Linear relationship between $Q/t$ and $(2A - C_{sIL})$ for norethisterone matrix-type intravaginal rings, with line gradient equal to $D_{sIL}C_{sIL}$, according to the Higuchi equation.

### Table 3

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>Melting point (°C)</th>
<th>mw (g mol$^{-1}$)</th>
<th>$D_{sIL}$, $C_{sIL}$ (mg cm$^{-1}$ day$^{-1}$)</th>
<th>$C_{sIL}$ (37°C) (mg cm$^{-3}$)</th>
<th>$D_{sIL}$ (cm$^{2}$ s$^{-1}$)</th>
<th>log $D_{sIL}$ (cm$^{2}$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLIN</td>
<td>142</td>
<td>425</td>
<td>0.00008</td>
<td>0.009</td>
<td>1.03$\times$10$^{-8}$</td>
<td>-6.99</td>
</tr>
<tr>
<td>E2</td>
<td>175</td>
<td>272</td>
<td>0.00038</td>
<td>0.004</td>
<td>1.10$\times$10$^{-6}$</td>
<td>-5.96</td>
</tr>
<tr>
<td>E3A</td>
<td>137</td>
<td>314</td>
<td>0.01715</td>
<td>0.237</td>
<td>8.38$\times$10$^{-7}$</td>
<td>-6.08</td>
</tr>
<tr>
<td>EDA</td>
<td>125</td>
<td>356</td>
<td>0.02976</td>
<td>1.310</td>
<td>2.63$\times$10$^{-7}$</td>
<td>-6.58</td>
</tr>
<tr>
<td>MET</td>
<td>159</td>
<td>171</td>
<td>0.00246</td>
<td>0.006</td>
<td>4.75$\times$10$^{-6}$</td>
<td>-5.32</td>
</tr>
<tr>
<td>NET</td>
<td>203</td>
<td>298</td>
<td>0.00151</td>
<td>0.015</td>
<td>1.17$\times$10$^{-6}$</td>
<td>-5.93</td>
</tr>
<tr>
<td>NETAc</td>
<td>161</td>
<td>340</td>
<td>0.02829</td>
<td>0.655</td>
<td>5.90$\times$10$^{-7}$</td>
<td>-6.30</td>
</tr>
<tr>
<td>OXY</td>
<td>57</td>
<td>357</td>
<td>0.21764</td>
<td>11.249</td>
<td>2.24$\times$10$^{-7}$</td>
<td>-6.65</td>
</tr>
</tbody>
</table>
ences observed in the IVR release characteristics of the various steroids (Table 2) are largely attributed to the differing silicone solubilities of these compounds. Clearly, acetylation of the hydroxyl groups of E2 and NET enhances silicone elastomer solubility. The relatively polar metronidazole and clindamycin (log $K_{ow}$ 0.0 and 2.0, respectively, compared with higher values of 3.9, 4.0, 5.0, 3.0, 4.0 and 4.0 for E2, E3A, EDA, NET, NETAc and OXY, respectively [29–31]) and the presence of two free hydroxyl groups in E2 contribute to their limited solubility in the hydrophobic silicone. Interestingly, the results suggest that acetylating metronidazole at its free hydroxyl group may produce a pro-drug with significantly enhanced silicone solubility and hence increased release rate compared to metronidazole itself, a pro-drug approach that has already been successfully adopted in the development of Galen Holdings’ estradiol-3-acetate IVR [10,18].

The dramatic differences observed in the silicone solubilities of the drug molecules can be attributed to the variations in chemical structure/functionality. According to the theory described earlier, the dissolution of a drug crystal in a polymer composition can be considered to consist of a dissociation step followed by a dissolution step. The former requires a dissociation energy and is dependent upon the melting temperature of the drug, according to Eq. (3) [20,32]

$$\log C_p = \text{constant} + \frac{\Delta H_d}{2.303RT_m}$$  (3)

where $C_p$ is the mole fraction solubility of the drug, $\Delta H_d$ is the drug lattice dissociation energy, $R$ is the gas constant, and $T_m$ is the drug melting temperature. The exponential relationship between the silicone solubility and the reciprocal of the melting point for the drugs of this study is demonstrated in Fig. 5.

From the values of $D_{sil}$, $C_{sil}$ and $C_{sil}$ (Table 3), the apparent silicone diffusion coefficients ($D_{sil}$) of the drugs in silicone have been calculated (Table 3). The silicone diffusion coefficient is described as ‘apparent’ in recognition of the fact that the diffusion process does not take place though a pure silicone polymer; the silicone elastomer base used to manufacture the IVRs includes a diatomaceous earth reinforcing filler which is known to influence the rate of diffusion of the permeating species by providing a surface for temporary Langmuir adsorption and creating a more tortuous diffusion pathway [33–35]. The diffusion coefficient values range from $1 \times 10^{-8}$ to $5 \times 10^{-6}$ cm$^2$ s$^{-1}$ and are similar to those reported for other diffusants in silicone elastomer systems [36–39]. The diffusion process can be considered as a ‘jumping’ mechanism wherein a solubilised penetrant molecule spends long periods of time (up to 1 ns) located within a pocket of free volume (a void) within the polymer structure before a temporary channel opens up with a neighbouring pocket. If the penetrant has a suitable velocity it may jump between the two pockets of free volume via the channel. The channel then closes and the permeant is entrapped within a different void. It is the rate and distance of this jumping motion that governs the rate of diffusion [40,41]. Intuitively, the molecular size/volume of the diffusant is likely to be an important factor in this diffusional process. Accordingly, a linear relationship ($R=0.952$) between the log of the apparent silicone diffusion coefficient (Table 3) and the relative molecular weight for each drug substance was observed (Fig. 6). Importantly, the graph allows the diffusion coefficient of any drug in MED-6382 silicone elastomer to be predicted with a reasonable degree of accuracy based solely on a knowledge of its molecular weight. (Of course, the diffusion coefficient will vary for other silicone elastomer formulations, which may have different degrees of
developed that will allow the prediction of daily flux rates for any new drug substance based solely on a knowledge of the molecular weight and melting temperature of the drug. Specifically, linear relationships were observed between the experimentally determined silicone diffusion coefficient and the drug molecular weight, and between the log of the experimentally determined silicone solubility and reciprocal melting temperature of the drug. The results will enable researchers to evaluate the potential of releasing new drug entities at therapeutic amounts from core and matrix type IVR devices.

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