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A dynamic mechanical method for determining the silicone elastomer solubility of drugs and pharmaceutical excipients in silicone intravaginal drug delivery rings

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Abstract

The silicone elastomer solubilities of a range of drugs and pharmaceutical excipients employed in the development of silicone intravaginal drug delivery rings (polyethylene glycols, norethisterone acetate, estradiol, triclosan, oleyl alcohol, oxybutynin) have been determined using dynamic mechanical analysis. The method involves measuring the concentration-dependent decrease in the storage modulus associated with the melting of the incorporated drug/excipient, and extrapolation to zero change in storage modulus. The study also demonstrates the effect of drug/excipient concentrations on the mechanical stiffness of the silicone devices at 37°C.

Keywords: Silicone elastomer solubility; Intravaginal rings; Dynamic mechanical analysis

1. Introduction

Silicone intravaginal rings (IVRs) are elastomeric, torus-shaped drug delivery devices (Fig. 1) designed to release drug(s) to the vagina [1–3]. The rings have, to date, been primarily developed for the systemic delivery of contraceptive steroids [1,4–7] and the localized and systemic delivery of steroids for hormone replacement therapy [1–3,8–10], although it is likely they will in the future be exploited for a much wider range of applications within women's health care including the delivery of anti-infective agents and HIV microbicides. Unsurprisingly, the IVR, which was *specifically* designed for the intravaginal administration of drugs, overcomes many of the disadvantages associated with more traditional vaginal drug dosage forms, such as gels, tablets and pessaries, which are often difficult to apply, interfere with intercourse and are poorly retained within the vagina [1]. However, the major advantage of the IVR is its ability and versatility in providing long-term, continuous release of drug(s) at constant pre-determined rates, thereby increasing cost-effectiveness, patient compliance and therapeutic efficacy [1].

Several designs of IVR have been developed, including matrix, reservoir and shell-type variants, each providing very different drug release profiles [1,4,11]. As with all diffusion/permeation-controlled delivery systems, the two major parameters influencing drug release rates from IVRs are the solubility and diffusivity of the drug in the silicone elastomer [1,3,12]. For example, Eqs. (1) and (2) model the release of drug under sink conditions from matrix- and reservoir-type IVRs, respectively, where Q is the release per unit area, t is time, A is the drug loading per unit volume in a matrix device, D_{SIL} is the effective silicone diffusion coefficient of the drug, C_{SIL} is the silicone solubility of the drug, and h is the thickness of the sheath layer in a reservoir device

$$Q = \sqrt{D_{SIL}(2A - C_{SIL})C_{SIL}t}, \tag{1}$$

$$Q = \frac{D_{SIL}C_{SIL}t}{h}. \tag{2}$$

These equations have been used to determine the silicone diffusion coefficient of certain steroidal drugs for intravaginal administration [3,13]. Briefly, a linear Q versus $\sqrt{t}$ or t release profiles is plotted whose gradient is a function of both D_{SIL} and C_{SIL}. Thus, if C_{SIL} is known, D_{SIL} can be determined easily. However, there are practical difficulties associated with directly

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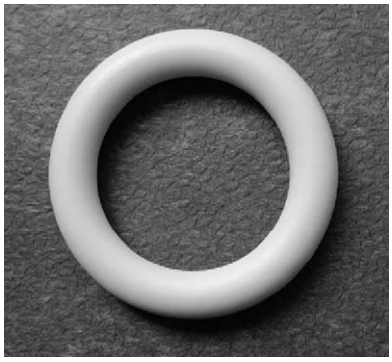

Fig. 1. Matrix-type silicone intravaginal ring. Dimensions: 54 mm external diameter, 9 mm cross-sectional diameter.

measuring the solubility of a species in a polymeric network. Unlike simple saturated solutions, it is impossible to filter the excess material from a drug-saturated polymer network. For this reason, approximation techniques are commonly employed. For example, the solubility of drugs in low molecular weight silicone oils has been widely used as an approximation to silicone elastomer solubility [3,13,14]. However, there are inevitably some compromises associated with this indirect approach to solubility determination. It is common practice to incorporate various quantities of finely ground fillers, such as diatomaceous earth, into silicone elastomers for IVR manufacture to improve their mechanical properties. The presence of fillers is known to decrease the effective silicone diffusion coefficient of steroidal drugs in silicone matrices as a result of the Langmuir adsorption of molecules onto the filler particles [15–17]. Also, drug solubility is expected to depend on both the network chain length and the degree of cross-linking. Clearly, these factors are not taken into account in the silicone oil solubility methodology.

In an attempt to overcome some of these compromises, alternative direct methods for determination of drug solubility in a silicone elastomer are required. Theeuwes at al. described a now widely used differential scanning calorimetry method for determining quantitatively the concentration of progesterone and cholesterol at their melting point in polydimethylsiloxane rubber [18]. Here we report a novel application of dynamic mechanical analysis (DMA) in the determination of silicone solubilities for a range of drugs and pharmaceutical excipients.

2. Experimental

2.1. Materials

Silicone elastomer base MED-6382, consisting of a mixture of high (10,000 Da) and low (2000 Da) molecular weight α,ω-hydroxy terminated poly(dimethylsiloxanes), a reinforcement filler (diatomaceous earth), a low molecular weight polydimethylsiloxane processing fluid (to modify viscosity for injection molding purposes), and tetrapropoxysilane (TPOS) were obtained from Nusil Technology (Carpinteria, USA). Stannous 2-ethyl-hexanoate (stannous octoate), 17β-estradiol (E2), oleyl alcohol (OA) and norethisterone acetate (NetAc) were purchased from Sigma (UK). Poly(ethyleneglycol)s (PEG) 1000, 2000 and 6000 and poly(dimethylsiloxane) 200® fluid were purchased from Aldrich (UK). Triclosan (TRIC) was purchased from CIBA Speciality Chemicals plc and oxybutynin free-base (OXY) was supplied by Orgamol (Evionnaz, Switzerland). All materials were used as received.

2.2. Preparation of the silicone strips

A 2 kg batch of the silicone elastomer mix was prepared by thoroughly mixing 2.5 parts by weight of TPOS with 100 parts of MED-6382 silicone elastomer base in a Kenwood Major food mixer for 30 min. Each of the following drugs or pharmaceutical excipients (polyethylene 6000, polyethylene glycol 2000, polyethylene glycol 1000, oxybutynin, triclosan, oleyl alcohol, norethisterone acetate, 17β-estradiol) was then hand-blended into 35 g samples of the silicone elastomer mix at various concentrations (1–20%, Table 1) to produce the active elastomer mix, which was then allowed to stand overnight to remove air entrapped during blending. One percent by weight of the curing catalyst, stannous 2-ethyl-hexanoate, was then added dropwise to the active silicone mixes and mixed for 30 s with a glass rod before injecting the mixes via a disposable 60 ml concentric-tipped plastic syringe into a specially manufactured aluminum mold of dimensions $12.75 \times 3.12 \times 200$ mm. The dimensions of the mold were chosen to match the sample constraints of the three-point bend clamp of the dynamic mechanical analyzer. The mold was placed in a pre-heated oven (80°C) for 5 min to allow the active silicone mix to cure. These conditions were selected to mimic a typical IVR manufacturing process. The cured elastomer strip was then removed from the mold, cut into sections approximately 30 mm in length and stored for 1 week at ambient conditions in preparation for DMA analysis.

2.3. Dynamic mechanical characterization

DMA is a technique that is employed in the structural analysis of viscoelastic materials, that is, materials displaying both elastic and dissipative components of deformation. The technique involves applying an oscillatory strain wave to a sample which results in an oscillatory stress response with a phase lag (δ) in between which is a measurement of the viscous contribution. A DMA 2980 dynamic mechanical

Table 1
Melting points and changes in storage modulus observed in the dynamic mechanical plots of storage modulus vs. temperature

Drug/excipient	Mean ± SD of observed melting point (°C)	Change in storage modulus $\Delta G'$ (MPa) (standard deviation, $n = 3$) % drug excipient concentration						
		1	2	5	7.5	10	15	20
PEG 6000	65.7 ± 0.7			1.72 (0.27)		4.21 (0.30)		7.81 (0.57)
PEG 2000	55.3 ± 5.0	0.09 (0.02)	1.04 (0.17)	2.64 (0.12)		4.63 (0.19)		
PEG 1000	35.4 ± 1.5	0.06 (0.02)	0.27 (0.04)	0.60 (0.05)		2.07 (0.18)		
Oxybutynin	59.0 ± 1.0	[a]	0.10 (0.01)	1.68 (0.23)	3.20 (0.19)		6.58	
Triclosan	62.2 ± 2.1	[a]	0.61 (0.07)	1.84 (0.45)		5.08 (0.30)		
Oleyl Alcohol	7.0 ± 2.7	0.02 (0.01)	0.45 (0.09)	1.05 (0.07)		2.68[b] (0.16)		
Norethisterone Acet.	153.5 ± 2.8	[a]		1.21 (0.15)		3.53 (0.40)		8.04 (0.42)
Estradiol	176.0 ± 4.4	1.52 (0.10)	1.87 (0.22)	4.37 (0.35)		7.29 (0.27)		

[a] No decrease in storage modulus observed for this sample.
[b] 9.4% oleyl acohol.

analyzer (TA instruments, Leatherhead, UK) was used to characterize the mechanical properties of the drug/excipient-loaded silicone strips. The silicone elastomer strips were mounted on a 3-point bend clamp, as illustrated in Fig. 2, the distance between the fixed clamp support bars being 20.00 mm. The sample was then periodically deformed using a static force of 0.010 N, an oscillatory amplitude of 200 μm, an oscillatory frequency of 1 Hz and an autotension of 150%. The autotension is the percentage of the static force needed to statically deform the sample by an amount equal to the oscillation amplitude. After establishing a reproducible response at ambient temperature, the sample was heated at 2°/min over a broad temperature range encompassing 37°C and the melt temperature of the drug/excipient. Three repetitions were made for each strip. The parameters measured were storage modulus (G'), loss modulus (G'') and tan δ.

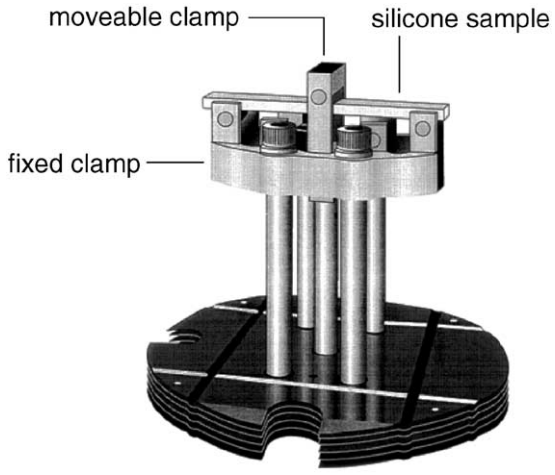

Fig. 2. Three-point bend clamp loaded with silicone elastomeric strip.

2.4. Solubility of excipients/drugs in low molecular weight polydimethylsiloxane fluid

The silicone solubility of the ultraviolet-active drugs/excipients (norethisterone acetate, estradiol and oxybutynin) was determined in triplicate according to a previously described UV-HPLC method [3]. Briefly, approximately 100 mg of each drug was added to 3.0 ml of poly(dimethylsiloxane) 200® fluid. After equilibration for 48 h at 37°C in an orbital shaker (Model $10 \times 400.XX2.C$, Sanyo Gallenkamp, Uxbridge,UK; 60 rpm, 32 mm orbit diameter) the saturated solutions were filtered at 37°C (Nalgene cellulose acetate filters, 0.2 μm) and 1.0 ml of the filtrate extracted into 100 ml acetonitrile. Drug solubilities in silicone were then determined by reverse phase HPLC. The Shimadzu HPLC system consisted of a model SIL-10AXL auto injector, 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, a model SPD-10A uv-vis detector and a

4.6 mm i.d. × 150 mm Luna 5 μm C18 column (Phenomenex, Cheshire, UK). HPLC analysis was performed at ambient temperature in isocratic mode, using an acetonitrile/pH 5 acetate buffer mobile phase delivered at 1.5 ml/min and 10 μl injection volumes. Specific parameters relating to each assay are: norethisterone acetate—85/15 mobile phase, 220 nm detection wavelength, 2.2 min retention time; estradiol—50/50 mobile phase, 281 nm detection wavelength, 2.0 min retention time; oxybutynin—45/55 mobile phase, 220 nm detection wavelength, 2.0 min retention time. The silicone solubilities of each drug were calculated using linear calibration curves produced by plotting peak areas versus concentration for a range of stock calibration solutions prepared in acetonitrile.

3. Results and discussion

Dynamic mechanical analysis is a versatile technique that may be used to simultaneously characterize both the mechanical and thermal properties of a wide range of polymeric materials of pharmaceutical and biomedical significance [19]. To date, it has been used to measure glass transition temperature, blend compatibility, mechanical moduli, damping properties and rates of curing. In this study, a novel DMA method for determination of the silicone elastomer solubility of a range of drugs and pharmaceutical excipients at their melting point is reported. The drugs chosen represent examples of therapeutic agents currently being evaluated for IVR development [1–4,8–10], while the choice of excipients includes materials being investigated in our laboratory for modifying drug release from the rings.

Representative plots of storage modulus vs. temperature are shown in Figs. 3 and 4 for NetAc and PEG 6000-loaded silicones, respectively. The other drug/excipient-loaded silicone samples produced similar plots. At higher drug/excipient loadings, G' is observed to decrease sharply at the drug/excipient melting point. Table 1 provides a summary of the mean decrease in storage moduli ($\Delta G'$) at the melt temperature for those samples in which it is observed. The coefficient of variation for the triplicate $\Delta G'$ measures was $<25\%$ for all samples, and typically $<12\%$. Fig. 5 shows representative plots of $\Delta G'$ vs. drug/excipient concentration for NetAc and PEG 6000-loaded silicones. Table 2 summarizes this information for all samples. The effect of drug/excipient concentration on the storage modulus at 37°C is shown in Fig. 6.

In Figs. 3 and 4, the effects on G' (a measure of the 'stiffness' of a material) of incorporating various concentrations of norethisterone acetate and polyethylene glycol 6000, respectively, are aptly demonstrated. The blank silicone matrix shows an increase (4.3–6.0 MPa) in G' over the temperature range. On

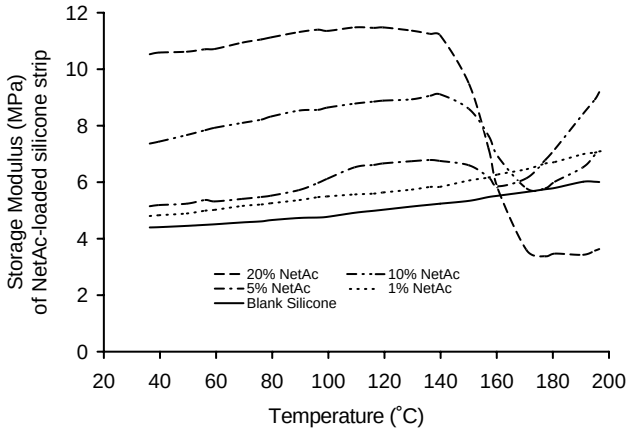

Fig. 3. Storage modulus as a function of norethisterone acetate concentration and temperature.

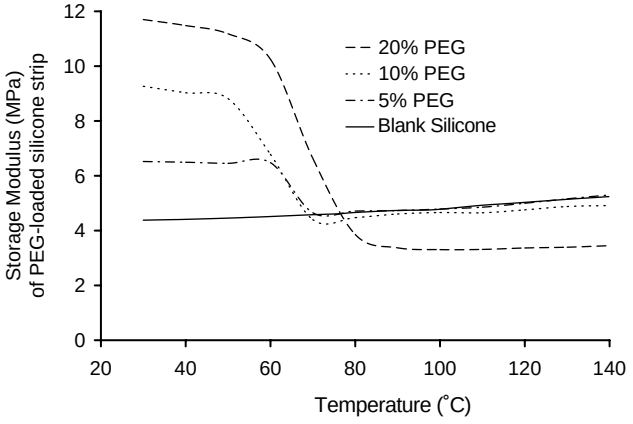

Fig. 4. Storage modulus as a function of polyethylene glycol 6000 concentration and temperature.

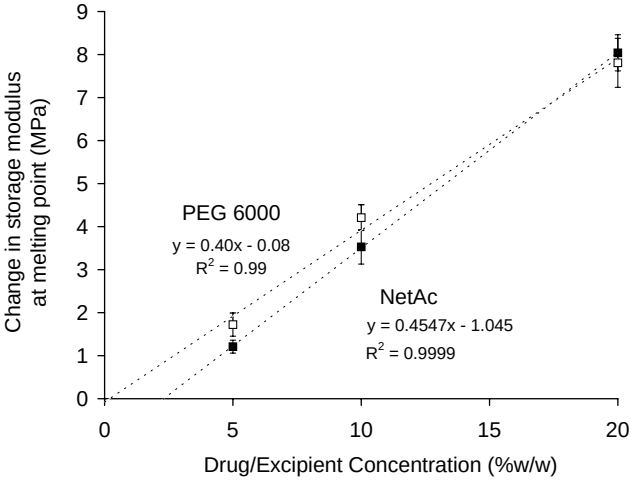

Fig. 5. Melt-associated decrease in storage modulus as a function of drug/excipient concentration for norethisterone acetate (NetAc) and polyethylene glycol 6000 (PEG 6000).

Table 2
Silicone elastomer and silicone oil solubilities of drugs and excipients

Drug/excipient	Gradient of best fit line	R^2 coefficient	X-axis intercept (solubility at mp, mg/g)	Mean silicone oil solubility ± SD (mg/g)
PEG 6000	0.40	0.99	1.9	—
PEG 2000	0.49	0.98	1.9	—
PEG 1000	0.22	0.96	11	—
Oxybutynin	0.50	1.00	15.6	10.696 ± 0.833
Triclosan	0.57	0.99	12.5	—
Oleyl alcohol	0.31	0.99	9.3	—
Norethisterone acet.	0.46	1.00	23	0.622 ± 0.041
Estradiol	0.66	0.99	−1.21	0.004 ± 0.001

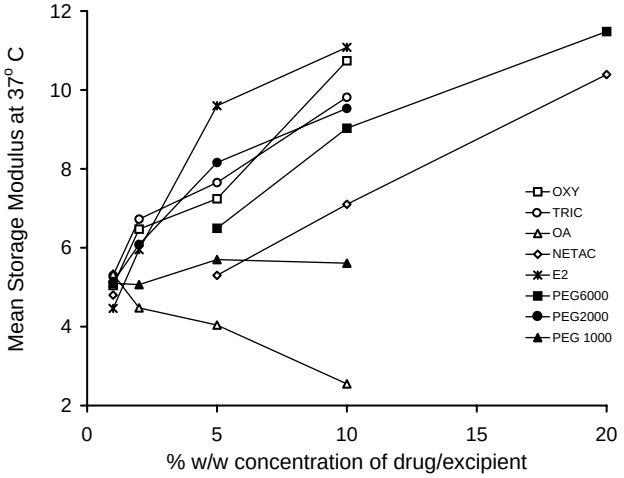

Fig. 6. Influence of drug/excipient concentration on the magnitude of the storage modulus of silicone elastomer at 37°C.

incorporation of 1% NetAc into the silicone elastomer, a similar trend when shifted to higher G' values is observed. The increase in G' with increasing NetAc concentration is also observed for the 5%, 10% and 20% NetAc samples. However, unlike the 1% sample, a discontinuity is observed at approximately 160°C in each plot, a temperature corresponding to the melt temperature of NetAc. The discontinuity cannot be attributed to any thermo-mechanical transitions of the silicone elastomer, as evidenced by the linear modulus–temperature plot for the blank silicones (Figs. 3 and 4). The insensitivity of storage modulus to temperature has been noted previously for silicone elastomeric denture soft lining materials [20]. Poly(dimethylsiloxane)s typically display a glass transition, a crystallization transition and a melting transition at approximately −120°C, −90°C and −40°C, respectively [21].

The magnitude of the discontinuity, as represented by the decrease in G' (Table 1), is clearly linearly proportional to the concentration of NetAc in the silicone elastomer (Table 2 and Fig. 5). Thus, in the 1% NetAc sample, all of the drug must be solubilized within the silicone elastomer near the melt temperature, since no melt-associated decrease in G' of the silicone elastomer is observed. At higher NetAc concentrations, a fraction of the drug remains undissolved giving rise to a concentration-dependent decrease in G' on melting.

By plotting $\Delta G'$ vs. NetAc concentration (Fig. 5), a straight-line relationship is observed whose x-axis intercept corresponds to the solubility of the drug in the silicone elastomer at the melt temperature. Similar linear, best-fit plots are observed for the other drug/excipient samples investigated ($r^2 > 0.96$), producing silicone elastomer solubilities of between 1.9 and 23 mg/g. These values are comparable with those obtained for cholesterol (35 mg/g, melting point 131°C) and progesterone (6 mg/g, melting point 129°C) using a related differential scanning calorimetry method [17]. Estradiol, whose exceptionally poor silicone solubility has prevented the development of an IVR capable of providing the clinically desired > 50 μg/day release rate required for estrogen replacement therapy [1–3], shows a negative solubility value (−1.21 mg/g, Table 2) as determined by the dynamic mechanical method. Such a negative value demonstrates the difficulty in using this technique for substances with very poor silicone solubility.

It is important to realize that the solubilities measured according to this dynamic mechanical method only apply at the melting point of the substance under investigation. Thus, for the high melting point drugs the calculated solubility is typically several orders of magnitude greater than the solubility determined in silicone oil at 37°C (Table 2). However, for the lower melting oxybutynin the DMA solubility value of 15.6 mg/g at 59°C relates well to 10.7 mg/g measured at 37°C in silicone oil.

In addition to the quantification of silicone elastomer solubilities, the results of the present study also demonstrate the effect of drug/excipient concentrations upon the mechanical properties of silicone devices. At body temperature, the two liquid excipients, PEG 1000 and oleyl alcohol, do not show the increasing stiffness (G') associated with increasing concentration of the

higher melting drugs/excipients (Fig. 6). In fact, increasing the PEG 1000 concentration has little influence on G', while increasing oleyl alcohol concentration shows a significant decrease in G'.

4. Conclusions

A novel dynamic mechanical method for determining the solubilities of drugs and pharmaceutical excipients in silicone elastomeric drug delivery devices is reported. The method has obvious advantages over other approximation methods in that the solubility is measured directly in the elastomer and thus includes effects associated with molecular weight, cross-linking density and the presence of filler. The disadvantage is solubility determination is measured at the drug/excipient melting point, rather than at body temperature. However, for drugs such as oxybutynin, similar values were obtained using the dynamic mechanical method and the silicone oil approximation method, suggesting that the dynamic mechanical method is well suited to substances whose melting point is close to body temperature.

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