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Release of anti-inflammatory drugs from a silicone elastomer matrix system

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Received July 20, 2008, accepted August 5, 2008

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Pharmazie 64: 19–25 (2009) *doi: 10.1691/ph.2008.8206*

The focus of the current study was to overcome the obstacles to incorporating non-steroidal anti-inflammatory drugs (NSAIDs) into a medical silicone elastomer and to investigate how the physicochemical properties of the drugs affect the curing process and drug release. Five representative NSAIDs were selected with different molecular weights and physicochemical properties. Silicone blends with 1% (w/w) drug in the sodium salt form could be obtained in a fully cured medical elastomer matrix whereas drugs in various other salt forms or the free acid form interfered with the curing process. The release rate was mainly dependent on the solubility in the drug-salt elastomer matrix, with ibuprofen sodium showing the fastest rate. These results indicate that inclusion of the NSAID salts in the silicone matrix does not change the microstructure or the permeability of the silicone matrix, and channel formation is minimal. The properties of NSAID-containing silicone blends are compatible with processes used for the manufacture of medical devices from silicone such as silicone stents or catheters, and could therefore be considered for such devices to reduce inflammation at the site of an implant and also for local delivery.

1. Introduction

Silicone elastomers are commercial polymers that have unique characteristics, such as biocompatibility and non-biodegradability, which make them suitable for medical use. They can be moulded into different shapes and are used to make catheters, stents, cardiac leads, respiratory aids and various other medical devices (Maeda et al. 2003, 2004; Malcolm et al. 2004). The use of silicone elastomers in implants has a long history, and their safety and reliability has been thoroughly investigated (Shastri 2002). Due to high chemical stability, devices made from silicone elastomers can easily be removed, unchanged, when the treatment has to be discontinued (Kajihara et al. 2000, 2003a; Shastri 2002).

Silicone has been used in drug delivery devices, such as intravaginal rings (Estring®), where the drug is loaded into a medical silicone elastomer matrix, Compudose® (silicone matrixes) and other drug delivery systems that release steroids (Hillery et al. 2001; Kajihara et al. 2000; Maeda et al. 2004).

Steroids and many other lipophilic drugs are easily compatible with silicone as the drug can be mixed into the liquid silicone blend before curing of the elastomer into the desired shape. Drug release from such non-degradable polymers is controlled by diffusion through the polymer matrix (Higuchi 1961). The amount of drug released is proportional to the square root of time (t). Ideally the release can then be described by the Higuchi equation (Eq. (1)):

$$Q_r = [D_s(2q_t - C_s)\, C_s t]^{1/2} \qquad (1)$$

where Q_r is the amount of drug released per unit area of matrix, q_t is the total amount of drug in a unit volume of matrix, C_s the solubility of drug in the polymer matrix and D_s is the diffusion coefficient for the drug in the matrix. Malcolm et al. (2003) observed that the release of eight lipophilic and somewhat hydrophilic steroidal, anticholinergic and antimicrobial drugs from silicone intravaginal rings followed the Higuchi equation. The measured solubility in silicone oil was used as a surrogate for solubility in the elastomer and it was shown that silicone oil solubility is a major factor in determining the release. Very hydrophilic drugs such as proteins do not dissolve or diffuse through silicone (Kajihara et al. 2000), but this can be addressed by mixing a water soluble excipient ($\geq$30%) with the silicone. Water-filled channels can then form in the silicone matrix through which the drug is released. Kajihara and co-workers developed a silicone-covered rod type formulation based on this principle. A similar approach was used for silicone-based matrix formulations for hydrochloride salts of papaverine and clonidine, where it was established that the release was through interconnected hydrophilic pathways (Carelli et al. 1995).

Medical devices made from silicone can be medicated by immersing them into a solution of the drug. This approach has been used for the antimicrobial-coated ventricular catheters for the prevention of catheter-related infection (Kohnen et al. 1998, 2003). However, a more practical approach would be to include the drug in the polymer resin before the silicone elastomer is moulded into the desired shape.

Fully-cured silicone elastomers are usually made from two liquid silicone blends, one containing a cross-linker and the other a catalyst. Mixing of these blends initiates the curing process, which is usually aided by heat (Fig. 1). Currently available medical silicones are cured with the

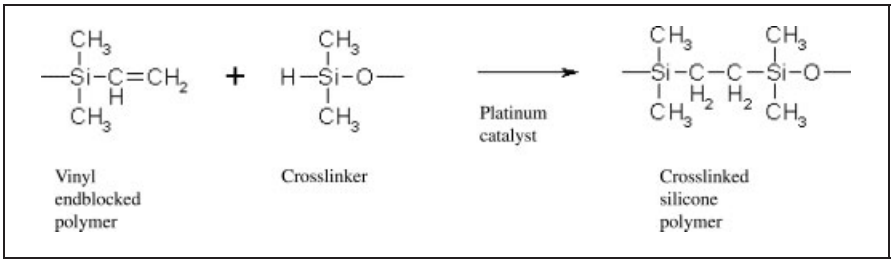

Fig. 1:
Curing of silicone, with platinum catalyst (there are no by-products generated in this process)

aid of a platinum catalyst, as the silicone curing process requires only very low levels of platinum catalyst for effective curing and the potentially harmful effect from leakage of catalyst is therefore minimised (Aguadisch and Colas 1997). This can limit the possibilities for producing drug-loaded elastomers with compounds that contain free amino or thiol groups, since these groups can form a strong complex with the platinum catalyst and therefore may inhibit or stop the curing process (Aguadisch and Colas 1997). Acetic acid is used as a curing inhibitor in some silicone products and carboxylic acids in general can have an inhibitory effect on the curing process.

The possibility of including NSAIDs in silicone elastomers is an interesting prospect for reducing inflammation at the site of an implant and also for local delivery. The challenge is to produce a silicone elastomer containing NSAIDs that has suitable properties, since the drugs in this class are all derivatives of carboxylic acids.

The focus of the current study was to overcome the obstacles to incorporating NSAIDs into medical silicone elastomer and to investigate how the physicochemical properties of the drugs affect the curing and drug release process. For the purpose of this study five representative NSAIDs were selected with different molecular weights and physicochemical properties. A suitable system for studying release was developed and the study focused on defining which parameters had major and minor contributions to the release properties for this class of drugs.

2. Investigations, results and discussion

2.1. Manufacturing silicone elastomer matrixes containing NSAIDs

Different forms of the NSAIDs were tested for the manufacture of silicone elastomer matrixes containing 1% (w/w) drug. Ibuprofen, diflunisal and ketoprofen in the free acid form prevented curing of the silicone blend which remained in the liquid form even after extensive heating. Thus it is probable that the platinum catalyst is poisoned by the carboxylic acid group that is common to these drugs. Some of the salt formulations of the NSAIDs needed to be produced. The ammonium salt of NSAIDs has been used in a commercial drug formulation (Voltaren® Emulgel) and other salts such as diethyl ammonium, tri-methyl ammonium and ethanol ammonium salts have been produced (Cheong and Choi 2003; Fini et al. 2005; Mashak and Taghizadeh 2006; Porzio et al. 1998; Sarveiya et al. 2004; Tantishaiyakul 2004) but these salts prevent curing of the silicone. These results might be expected since it is well known that tin, sulphur, and some amine-containing compounds may permanently inhibit the curing process (Aguadisch and Colas 1997).

However, some curing was observed when tetramethyl ammonium and potassium salts of ibuprofen were mixed into the silicone blend, although the resulting silicone elastomers were semi-solid and lacked elasticity. Sodium salt on the other hand worked much better, in that a fully cured elastomer was formed with all of the NSAIDs and there was only a slight increase in the force needed for 100% and 200% elongation compared to a drug-free silicone elastomer (Table 1). Therefore sodium salts were used to manufacture the silicone matrixes.

Elastomers containing sodium salts of NSAIDs are slightly more opaque than elastomers that do not contain drugs, indicating that the drug is present in the form of dispersed solid particles and is only partially dissolved in the cured silicone elastomer.

2.2. Receptor medium

In previous studies on silicone elastomer based drug delivery matrixes, phosphate-buffered saline ((PBS) pH 7.4) (Kajihara et al. 2001; Maeda et al. 2004), phosphate buffer (pH 5 and 7.4) (Malcolm et al. 2003), tween20/PBS (Maeda et al. 2003, 2004), methanol/water (Maeda et al., 2004), ethanol/water (Mashak and Taghizadeh 2006) or acetate buffer (Malcolm et al. 2004) and benzalkonium chloride (Malcolm et al. 2003) have been used as a receptor medium. One requirement for the receptor phase is that the solubility of the drug should not be a limiting

Table 1: Average drug release, solubility, diffusion parameters and tensile force (± standard deviation) of silicone matrixes (n = 3)

Drugs*	Flux rate $\frac{Q}{t^{1/2}}$ $\left(\frac{mg}{cm^2 \cdot h^{1/2}}\right) \times 10^{-3}$	C_s $\left(\frac{mg}{cm^3}\right) \times 10^{-3}$	D_s $\left(\frac{cm^2}{h}\right) \times 10^{-3}$	Tensile force (N) Elongation	
				100%	200%
Without				2.23 ± 0.07	3.72 ± 0.10
Na-IBU	42.5 ± 2.4**	42 ± 2.7	1.69 ± 0.11	2.42 ± 0.38	4.03 ± 0.76
Na-NAPR	8.9 ± 0.6**	20 ± 3.2	0.16 ± 0.03	2.91 ± 0.19	4.83 ± 0.07
Na-KETO	7.1 ± 0.3**	4.2 ± 5.1	0.48 ± 0.58	3.39 ± 0.06	5.48 ± 0.09
Na-DICLO	2.8 ± 0.5**	0.6 ± 0.03	0.52 ± 0.03	2.43 ± 0.06	3.98 ± 0.11
Na-DIFL	1.2 ± 0.2**	0.2 ± 0.1	0.26 ± 0.13	2.69 ± 0.09	4.49 ± 0.13

* The Drug salts used were: ibuprofen sodium (Na-IBU), naproxen sodium (Na-NAPR), ketoprofen sodium (Na-KETO), diclofenac sodium (Na-DICLO), diflunisal sodium (Na-DIFL)
** $R^2 > 0.996$

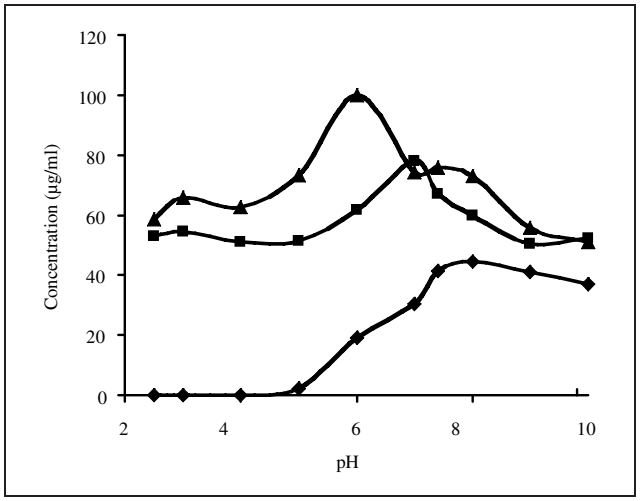

Fig. 2: Release of 1% (w/w) Na-IBU from silicone elastomer, over 7 days, at different pH values of the receptor medium containing 0% (w/v) (◆), 2.5% (■) and 7.5% (▲) HPβCD

factor. The receptor phase should also be inert, i.e. it should not affect the properties of the matrix system. Sodium salts of NSAIDs can be slightly soluble in water (according to PhEur), therefore a solubilising agent must be added to the receptor phase or the pH adjusted for the NSAIDs in order for them to be released from the silicone elastomer. Using methanol as a receptor medium causes a dramatic increase in drug release rate, compared to simple phosphate buffer, with just over a 10-fold increase in drug release and even more with ethanol (>50-fold increase). However, further studies have shown that a short pre-treatment with methanol or ethanol solution also increases the release into the aqueous phase over a certain period, indicating that the alcohols are absorbed into the elastomer and significantly affect the release properties. These simple alcohols are therefore not sufficiently inert to be used to solubilise the drug in the receptor phase. Cyclodextrins are cyclic oligosaccharides that have been used as solubilising agents in drug formulations and in drug release and permeation studies (Loftsson et al. 2002a, b, 2005). Cyclodextrin derivatives, such as HPβCD (hydroxypropyl-β-cyclodextrin), are large hydrophilic molecules that do not penetrate into lipophilic membranes (Loftsson and Masson 2001) such as silicone. Release studies were conducted with receptor medium at different pH levels (Fig. 2), with different weight per weight (w/w) percentages of HPβCD (0, 2.5 and 7.5%) for determination of the most suitable receptor medium.

The release of ibuprofen was highly pH-dependent when using a plain buffer as the receptor medium (Fig. 2) and the solubility of the drug became a limiting factor at low pH. The pH had much less effect when the receptor phase contained HPβCD. The solubility of ibuprofen is approximately 12.4 mg/mL and 22.9 mg/mL at 2.5 and 7.5% HPβCD concentration respectively (Loftsson et al. 2002a), and the solubility is therefore not limiting in this case. Interestingly, though the difference was small there was still some effect of the pH with maximum release at pH 6 and 7 for the 2.5 and 7.5% solutions respectively. The cyclodextrin concentration had only a small effect on drug release and the difference was not significant at pH 7.4. Phosphate buffer with 2.5% cyclodextrin concentration and pH adjusted to 7.4 was used in subsequent studies.

2.3. Determination of diffusion coefficient with lag time (t_{LAG})

Malcolm et al. (2003) showed that release of neutral lipophilic drugs from silicone matrix systems depends primarily on the silicone elastomer diffusivity (D) and solubility (C_s) of the drug molecule in the silicone elastomer.

The diffusivity parameter can be determined from a permeation experiment where flux of the drug through a silicone membrane is measured. Saturated solutions of the NSAIDs were placed in a donor chamber of Franz diffusion cells, and the concentration of the drug in the receptor phase measured at fixed intervals until a steady state flux rate was established according to Ficks law:

$$\frac{dQ}{dt} = \frac{D \cdot K \cdot A \cdot C_d}{h} \qquad (2)$$

where dQ/dt is the flux rate, D is the diffusion coefficient, K is the partition coefficient, C_d is the concentration of the donor medium, A is the surface area over which diffusion is taking place and h is the membrane thickness. Some time is required to establish the steady-state condition and the time is dependent on the rate of diffusion. The lag time (t_{LAG}) obtained from the extrapolation of a straight line fit of steady-state data against the time axis (Fig. 3) can then be used to calculate the diffusion coefficient, according to (Sinko and Martin 2006):

$$D = \frac{h^2}{6 \cdot t_{LAG}} \qquad (3)$$

Results from these experiments and the physicochemical properties of the drugs are presented in Table 2. The highest trans-membrane flux was observed for Na-IBU (ibuprofen sodium) which has the lowest melting point and molecular weight (MW), whereas the lowest flux was observed for Na-DIFL (diflunisal sodium). The diffusion coefficient, determined from the lag time, was also higher for Na-IBU. However the variability, in this case, was also high and the effect of the difference in the diffusion coefficient on the flux difference could not be readily determined from this data. The steady state flux should be proportional to $K \times C_d = C_{o(membrane)}$ which is the equilibrium concentration of the drug in the silicone membrane at the surface where it is in contact with the donor phase. If C_d is the saturation concentration in the donor phase then the silicone membrane will also be saturated at this surface and $C_{o(membrane)} = C_s$ which is solubility of the

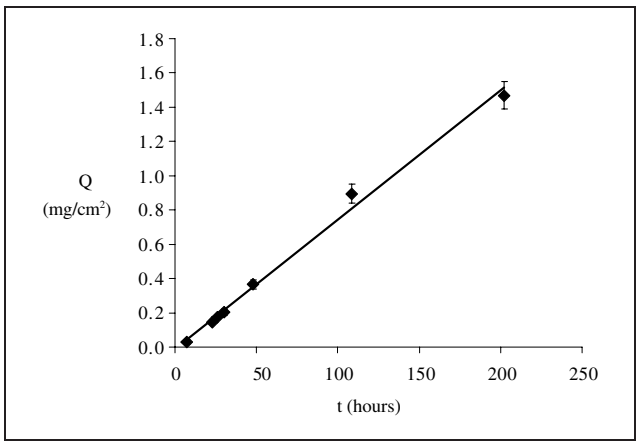

Fig. 3: Flux from a saturated ibuprofen solution (n = 3) through drug-free silicone elastomer membrane. The lag time is determined by extrapolating the steady state portion of the line to the time axis (the point of intersection on the × axis is the lag time)

Table 2: Physicochemical properties of NSAIDs, flow rate and diffusion (± standard deviation (n = 3))

Drug	Melting point (°C)	MW $\left(\frac{g}{mol}\right)$	Flux $\frac{Q}{t}$ $\left(\frac{mg}{cm^2 \cdot h}\right) \times 10^{-3}$	t_{LAG} (h)	D $\left(\frac{cm^2}{h}\right) \times 10^{-3}$
Na-IBU	104–106	228.27	7.53 ± 0.21*	1.2 ± 1.0	9.3 ± 11.2
Na-NAPR	250–251	252.24	0.30 ± 0.03*	18.8 ± 1.6	0.35 ± 0.04
Na-KETO	184–186	276.27	0.58 ± 0.03*	27.3 ± 0.8	0.24 ± 0.01
Na-DICLO	283–285	318.14	0.11 ± 0.003*	9.0 ± 1.9	0.73 ± 0.14
Na-DIFL	350	272.18	0.10 ± 0.02*	41.8 ± 2.8	0.16 ± 0.01

$R^2 > 0.867$

drug in the silicone membrane. In general, solubility is expected to decrease as the stability of the crystal and the melting point increases. The flux shown in Table 2 decreases as the melting point of the drug salt increases. Solubility of the drug in the silicone membrane therefore appears to be an important factor.

2.4. Solubility of the NSAIDs in silicone oil

The drug solubility was determined in low viscosity silicone oil (Table 1). It was not feasible to inject the silicone oil into the HPLC apparatus and therefore it was necessary to extract the drug from the saturated silicone oil. Emulsions were formed when extraction was attempted with the HPLC mobile phases. It was difficult to separate these emulsions and this approach was therefore abandoned. Extraction with carbonate buffer pH 10.0 was not efficient. Previously we have shown that 10% (w/v) aqueous HPγCD (hydroxypropyl-γ-cyclodextrin) can be used for efficient extraction of lipophilic compounds from the organic phase (Masson et al. 2005, 2007). This worked well with the silicone oil. After each extraction of the drug the remaining silicone oil was washed two times with little to no drug in the second washing phase. This method was used to determine solubility in the silicone oil (Table 1). There was more than a 200-fold difference in solubility between the most soluble drug salt (Na-IBU) and the least soluble drug salt (Na-DIFL). Drug solubility in the elastomer may depend on the degree of cross-linking and network chain length, but solubility in low viscosity silicone oil should be a suitable surrogate and this solubility should correlate well with the relative solubility in the silicone elastomer. Solubility of Na-IBU and Na-DICLO (diclofenac sodium) in silicone oil was also measured at 37 °C and 50 °C. There was no significant difference between room temperature (42 ± 2.7) and 37 °C (41.3 ± 1.2) for Na-IBU, but solubility increased about 1.5 times at 50 °C (60.9 ± 2.8) compared to room temperature. For Na-DICLO solubility increased about 3 times from room temperature to 50 °C (0.6 ± 0.03 at room temperature, 1.6 ± 0.6 at 37 °C and 2.0 ± 0.7 at 50 °C).

2.5. Release study and determination of the diffusion coefficient

According to Higuchi, under ideal conditions where dissolution or depletion of the drug is not a limiting factor the drug release rate can be described by Eq. (1). For a given system dQ/dt can then be obtained from a straight line plot of Q vs. $\sqrt{t}$. If q_t and C_s are known then we can calculate D_s according to Eq. (4):

$$D_s = \frac{Q^2}{(2q_t - C_s)\, C_s t} \qquad (4)$$

The calculated Q and D_s are reported in Table 1. This diffusion coefficient could be estimated by two independent indirect methods: the membrane permeation study (D) and the release study (D_s). These estimates are based on the assumption that the salts dissolved and were transported through the silicone polymer matrix and that the dissolution of the drug is not a limiting factor.

The variation in the diffusivity values calculated according to the two methods was only slightly significant for Na-DICLO and significant for Na-NAPR (naproxen sodium). For the other drugs the difference was not significant. The correlation between these two indirect methods was very good, given experimental error and the fact that conditions are never ideal.

Previous studies (Kajihara et al., 2003a, b; Maeda et al. 2003) have reported the development of silicone-based rod type matrix systems in which the drug release from silicone can lead to channel formation in some instances for both water soluble and lipophilic drugs, thus increasing drug release. Adding salt to the silicone matrix increases formation of channels in the silicone elastomer.

These current results indicate that the inclusion of the NSAID salts in the silicone matrix does not change the microstructure or the permeability of the silicone matrix and that there is minimal channel formation. The release rate was highest for the Na-IBU matrixes or 35 times faster than release from Na-DIFL matrixes, which showed the slowest rate of release. This difference in diffusivity between the two drugs is about 6-fold (according to D_s) and thus only partially explains the difference (by the square root of 6). Malcolm et al. (2003) showed that there was a strong inverse correlation between log D_s and the molecular weight (MW) of neutral lipophilic drugs. No correlation was found for the NSAID salts in the present

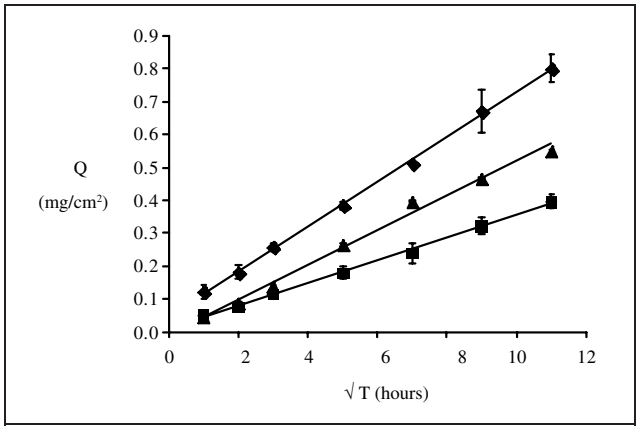

Fig. 4: Release of 1% (w/w) Na-IBU at 25 °C (▲), 37 °C (■) and 50 °C (◆) measured in side-by-side cells (n = 3)

Table 3: Flux rates (± standard deviation) of Na-IBU at different temperatures (n = 3)

Temperature	$\frac{Q}{t^{1/2}}\left(\frac{mg}{cm^2 \cdot h^{1/2}}\right)$	
°C	0.5% (w/w)	1% (w/w)
25	0.0314 ± 0.0033	0.0345 ± 0.0025
37	0.0352 ± 0.0111	0.0560 ± 0.0057
50	0.0601 ± 0.0043	0.0680 ± 0.0033

study ($R < 0.0679$). Thus it was not sufficient to know the MW of the salt in order to predict D_s.

Na-IBU with a low melting point had more than 210 times higher solubility in the silicone oil than Na-DIFL with a high melting point. The difference in release rates can therefore mainly be explained by the difference in solubility in the silicone matrix. In general there was good correlation between release rate and solubility in the silicone oil.

Temperature should affect the release rate as the solubility and the diffusion coefficient will be affected by temperature. The side-by-side cell setup was used to investigate the release from the Na-IBU matrix systems as a function of temperature (Fig. 4). Table 3 shows that elevated temperature increased drug release. According to a paired sample T test, there was a statistically significant ($p < 0.05$) increase in drug release over time.

In Conclusion, we have investigated the possibility of preparing NSAID-containing silicone elastomer drug-delivery matrixes from medical silicone with properties comparable to silicone elastomers used for medical devices. NSAID drugs in the acid form interfered with the curing process. Silicone blends with 1% (w/w) drug in the sodium salt form could be cured to obtain a fully cured elastomer matrix whereas drugs in various other salt forms interfered with the curing process. Aqueous HPβCD solution was a suitable receptor phase that could be used to measure the release over a broad pH-range. The release rate was mainly dependent on the solubility in the drug-salt elastomer matrix, with Na-IBU showing the fastest release. These results indicate that the inclusion of the NSAID salts in the silicone matrix does not change the microstructure or the permeability of the silicone matrix and channel formation is minimal. The properties of NSAID-containing silicone blends are compatible with processes used for the manufacture of medical devices from silicone such as silicone stents or catheters, and could therefore be considered for such devices to reduce inflammation at the site of an implant and also for local delivery.

3. Experimental

3.1. Materials

Silicone elastomer MED-4901 was obtained from Nusil (Carpinteria, USA), HPγCD was obtained from Wacker Chemie (Adrian, USA) and HPβCD Kleptose from Roqette (Lestrem Cedex, France). Ketoprofen (KETO), ibuprofen sodium (Na-IBU), diclofenac sodium (Na-DICLO), potassium hydroxide, trimethyl ammonium, polyethylene glycol, dimethylpolysiloxan 20 cSt, HPLC grade acetonitrile and methanol were purchased from Sigma-Aldrich (St. Louis, MO, USA). Naproxen sodium (Na-NAPR) was obtained from Lyfjaverslun Íslands (Reykjavik, Iceland). Diflunisal (DIFL) was purchased from ICN Biomedicals Inc. (Solon, OH, USA). Tetramethyl ammonium, diethyl ammonium, monoethanol ammonium, sodium hydroxide and potassium dihydrogen phosphate were purchased from Merck & Co., Inc. (Whitehouse Station, NJ, USA). Ethanol and acetic acid were purchased from Riedel-deHaën (AG Seelze, Germany). Deionised water for the HPLC mobile phase was obtained by a Milli-Q purification system (Millipore, Billerica, MA, USA).

Table 4: HPLC assays

Drug	Mobile phase	Det. λ (nm)
IBU	CH_3CN-H_2O-AcAc (60 : 39.6 : 0.4)	230
KETO	CH_3CN-H_2O-AcAc (60 : 39.6 : 0.4)	254
DICLO	CH_3CN-H_2O-AcAc (60 : 39.6 : 0.4)	282
NAPR	CH_3CN-H_2O-AcAc (65 : 34 : 1)	254
DIFL	CH_3CN-H_2O-AcAc (65 : 34 : 1)	254

3.2. Salts of NSAIDs and micronising

Sodium hydroxide (2.00 g, 0.050 mol) was dissolved in 100 ml of ethanol (NaOH-EtOH). Sodium salts of ketoprofen and diflunisal were produced by dissolving the drug in ethanol and adding an equimolar quantity of NaOH-EtOH under stirring, followed by evaporation of the solvent, and drying in an oven (40 °C) for 2 h. The resulting amorphous solids were crystallised by controlled precipitation from 96% ethanol, then dried for two days at room temperature and for a further two days in an oven (40 °C) (Hildebrand and Müller-Goymann 1997).

Potassium hydroxide, tetramethyl ammonium, trimethyl ammonium, diethyl ammonium and monoethanol ammonium salts were produced by adding an equimolar quantity of the amine or hydroxyl salt to a methanolic solution of the NSAID under stirring, followed by evaporation of the solvent. The product was then dried, in a glass desiccator, for two days at room temperature and micronised through a 150 μm strainer.

3.3. High-performance liquid chromatographic analysis

HPLC analyses were conducted using a LDC analytical solvent delivery system (Consta Metric® 3200), variable wavelength detector (Spectro Monitor® 3200) automatic sampler (Merck Hitachi AS-4000 A Intelligent Autosampler) and an integrator (IgorPro 4). Supelcosil TMLC-18-DB column (4.6 × 150 mm, 5 μm) and OnyxTM Monolithic C18 column (4.6 X 100 mm, 5 μm) with flow-rate of 1.5 mL/min. HPLC assays were used to measure drug solubility in silicone oil and drug release (section 2.3–5.). Table 4 details the HPLC assay conditions for each drug.

3.4. Preparation of silicone matrix-type system

Silicone elastomer MED-4901 is supplied as a two-component kit (parts A and B). Part A contains a platinum catalyst and part B contains cross-linker and cure inhibitor. Part A and part B were combined in a 1 : 1 ratio and mixed with the drugs in a speed-mixer (Planetary mixer/deaerator Mazerustar) for 100–200 s and the mixtures were then poured into a circular aluminium mould (diameter 170 mm and thickness 2 mm). The mixtures in the moulds were degassed under vacuum for 1 h and then the mould was closed with a lid (where excess silicone was forced out through openings in the lid). The moulds were placed in a pre-heated oven (110 °C) for 2–4 hours to cure the silicone mixture. The silicone elastomer matrix systems (silicone membranes) were stored at room temperature before use. Drug loadings are presented as percentage total weight of MED-4901, 1 : 1 mix of part A and B, (w/w) relative to the neutral form of the drugs.

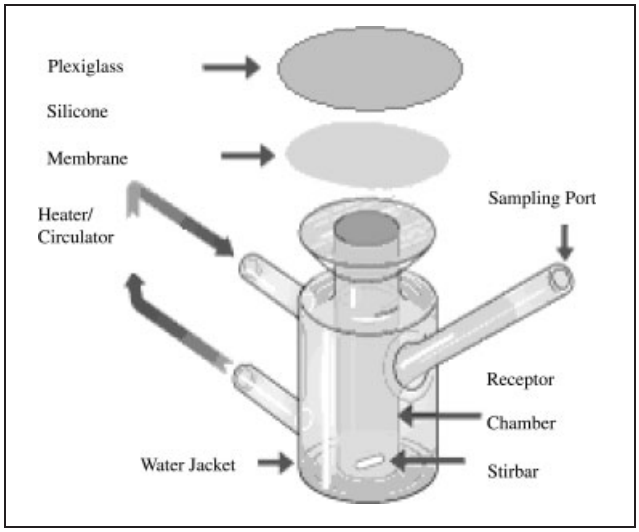

Fig. 5: Franz Diffusion Cell. Image modified and published with permission of PermeGear (www.permegear.com)

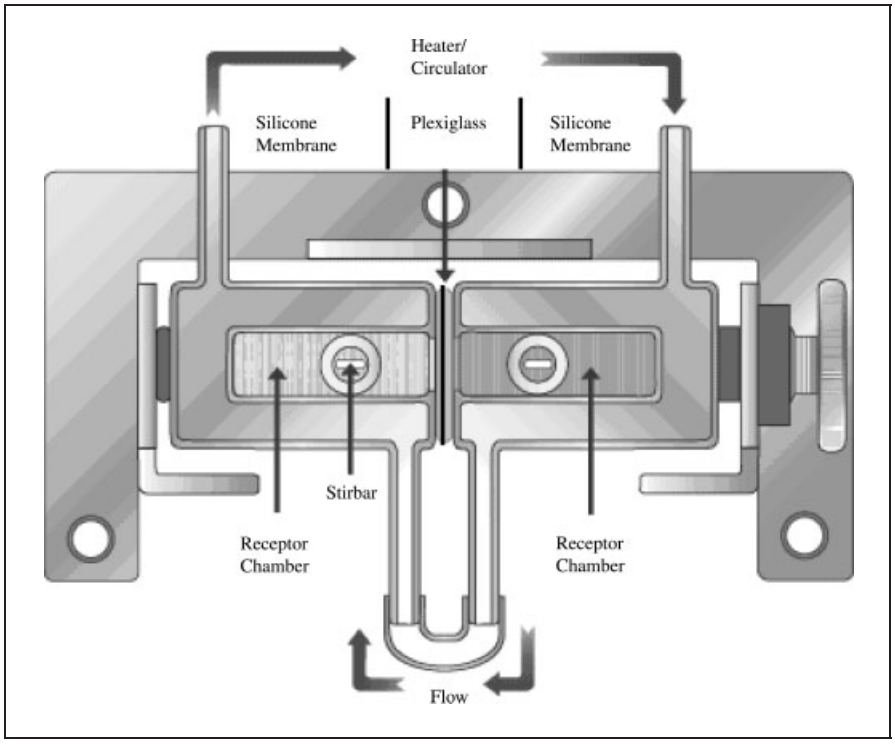

Fig. 6:
Side-By-Side cell. Image modified and published with permission of PermeGear (www.permegear.com)

3.5. Drug solubility in silicone oil

Low viscosity silicone oil (dimethylpolysiloxan, 20 cSt) was used as a surrogate for the silicone elastomer (Malcolm et al. 2003, 2002, 2004; Russell et al. 2000). Six mL of silicone oil and 200 mg of each drug were shaken in an orbital shaker (Edmund Bühler GmbH) for 14 days at room temperature. The saturated silicone oil was filtered through a 0.45 μm filter (Schleicher & Schuell, FP 30); 2.0 mL of the filtered silicone was then extracted with 3 × 1.0 mL of 10% HPγCD. The drug concentration in the extracts was determined by HPLC. The concentration of the drug in the silicone oil was calculated from the total quantity of the drug in the three extracts. The drug concentration in the last extract was below the limit of quantification or less than 2% of the drug in the first extract. This confirmed that all drug was extracted into the aqueous phase.

3.6. Flux through silicone membrane

Saturated solutions of the drugs in phosphate buffer, pH 7.4 (50.0 mL of 0.2 M potassium dihydrogen phosphate combined with 39.1 mL of 0.2 M sodium hydroxide and diluted to 200.0 mL with water) were prepared by shaking in a closed vessel, with an excess amount of a sodium salt of the NSAID, on an orbital shaker for 2–3 of days. The pH was measured and corrected by addition of NaOH (4 M) and shaking continued until the pH was stable.

Drug-free silicone membrane (diameter 32 mm) was clamped between the donor and receptor chambers of a Franz diffusion cell (Permegear, Inc, Hellertown, PA, USA) with 12 mL cell volume (membrane surface area of 1.77 cm^2 and a cell volume of 12 mL). The donor phase consisted of 2 mL of filtered saturated NSAID solutions and the receptor phase was phosphate buffer, pH 7.4 with 2.5 % (w/v) HPβCD (the receptor medium), which was stirred at 400 rpm. Aliquots (100 μL) were withdrawn from the receptor compartment at predetermined time intervals, and replaced with an equal volume of fresh medium. The samples were analysed by HPLC to determine the quantity of drug that had penetrated through the silicone membrane.

3.7. In vitro release studies from silicone matrixes

Drug-containing silicone membrane matrixes were cut into smaller circles (diameter 32 mm). In vitro release studies were conducted with Franz diffusion cells (membrane surface area of 1.77 cm^2 and a cell volume of 12 mL). A plexiglas-plate was placed on top of the membrane and to prevent diffusion of air through the membrane into the receptor phase (Fig. 5) instead of the donor chamber. For the side-by-side cells (Permegear, Inc., Hellertown, PA, USA), with temperature-controlled water jackets, (membrane surface area of 1.13 cm^2 and a cell volume of 3.4 mL), a plexiglas plate was used to separate two silicone matrixes (Fig. 6). Phosphate buffer, pH 7.4 with 2.5% (w/v) HPβCD (unless otherwise indicated), was used as the receptor medium, with stirring at 400 rpm. Aliquots (100 μL) were withdrawn from the receptor compartment at predetermined time intervals, and replaced with an equal volume of fresh medium. The samples were analysed by HPLC to determine the quantity of drug that had been released from the silicone matrix membrane.

3.8. Tensile strength

The strength of the silicone membranes (15 mm × 40 mm) was measured in a Stable Micro System, Texture Analyser TA-XT2i. Force was measured in Newtons (N), for 1% drug-loaded silicone membranes and drug-free silicone. Parameters were set to a distance of 40.0 mm, test speed of 10.0 mm/s, force of 0.981 N, time to 5.00 s. and load cell of 5 kg.

Acknowledgements: Financial support from the Iceland Research Centre, Technical Development Fund, the Bergþóru and Þorsteins Scheving Thorsteinssonar Fund and the University of Iceland Research Fund is gratefully acknowledged.

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