Bringing Silicone To New Levels

Martin Alm*, BioModics, Stengårds Allé 31A, DK-2800 Lyngby, Denmark, martinalm01@gmail.com

ABSTRACT
The speech will include a brief introduction to the physical properties of carbon dioxide (CO_2). The tunability of the physical properties of CO_2 combined with the unique nature of silicone rubber result in a thermodynamic favorable situation where it is possible to alter the properties of the silicone rubber by impregnation of different substances. In many medical devices silicone rubber has found its use due to desirable properties such as chemical inertness and high flexibility. One application is as drug delivery devices. However, due to silicone rubbers hydrophobic nature the type of drugs that can be released are rather limited. One way to overcome this is to change the chemistry of the silicone rubber. BioModics' approach is to produce interpenetration polymer networks (IPNs) of silicone rubber and hydrogel material in supercritical CO_2. The impregnated hydrogel material functions as a reservoir and transport facility inside the matrix. This method widens the range of drugs that can be released from silicone rubber to include hydrophilic drugs, such as silver ions, sulfonamides and antimicrobial peptides.

INTRODUCTION
Interpenetrating polymer networks are defined as a polymer blend comprising two or more networks which are at least partially interlaced on a molecular scale but not covalently bonded to each other and cannot be separated unless chemical bonds are broken. Injection moulded silicone elastomers (LSR) are applied as substrate material, a hydrophilic monomer is impregnated into the substrate material using supercritical carbon dioxide (scCO2) as an auxiliary solvent to assist the impregnation process. Then the guest monomer is polymerized and optionally cross-linked.[1]

When HEMA is impregnated, polymerized and cross-linked inside the silicone rubber matrix the properties of the material is affected. The resulting IPN will have properties different from those of the virgin silicone rubber and the cross-linked PHEMA. In order to describe and test the boundaries of the system it is convenient to examine how the PHEMA content in the IPN affects different properties. In the present paper the water uptake and the mechanical properties in terms of elongation at break and tensile strength, of IPNs with different PHEMA content are examined. Furthermore it is examined how the concentration of HEMA in the feed affects the PHEMA content in the resulting IPN.

IPNs can be applied as drug delivery devices. The substrate material of the IPN is considered to be silicone rubber, and the guest polymer a hydrogel material. The IPN then becomes the substrate material for a drug delivery device. For the loading process supercritical carbon dioxide (scCO2), organic solvents and water or mixtures thereof might be applied as solvents. The system is illustrated in figure 1. The IPN is placed in a solvent that contains the drug, either dissolved or partly dissolved. As the IPN is swelled in the solvent containing a concentration of drug ([drug]),

the drug will be transported into the matrix. According to the choice of solvent either the silicone part or the hydrogel part or both are swelled in the solvent, and hence loaded with drug.

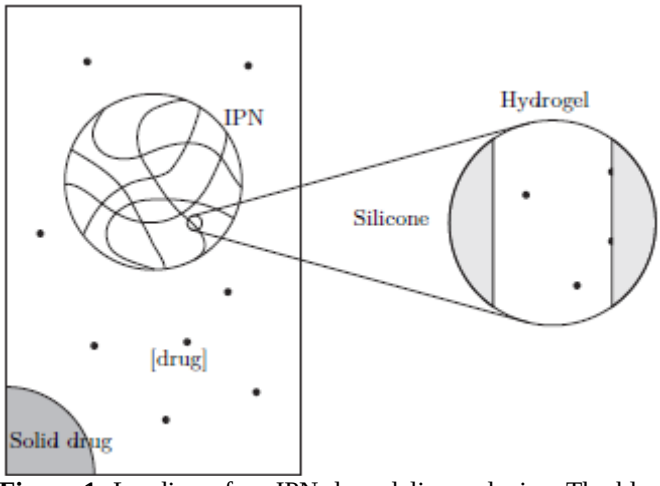

Figure 1: Loading of an IPN drug delivery device. The black dots represent dissolved drug. As can be seen in the enlarged view drug is adsorbed inside the matrix.

After the sample is loaded, it is immersed in a nutrient medium and either the biological effect or the drug release are monitored. Different types of drugs have been applied with the IPN system with success such as ionic silver, sulfonamides and antimicrobial peptides.

MATERIALS AND METHODS

Chemicals:

98% 2-hydroxyethyl methacrylate (HEMA) with 200 ppm monomethyl ether hydroquinone (MEHQ) as inhibitor supplied by Acros Organics (Belgium) is passed through an inhibitor remover disposable column (Cat no. 306312) supplied by Aldrich (USA) for removal of inhibitor. HEMA is then purified by distillation at reduced pressure, and the fraction at approx. 67°C and 3.5 mbar is collected and stored at 5°C under an argon atmosphere. A 0.2 M diethyl peroxydicarbonate (DEPDC) in hexane solution is prepared as described below and applied as initiator. 98% ethylene glycol dimethacrylate (EGDMA) supplied by Aldrich (USA) is used as cross-linking agent, 99.9% ethanol supplied by Merck (Germany) and CO_2 N48 supplied by Air Liquide Denmark A/S (Denmark), 98% ethyl chloroformate and molecular sieve UOP type 13X supplied by Fluka Chemie (Switzerland), NaOH pellets and 30% H_2O_2 supplied by Bie & Berntsen (Denmark) are all used as received.

Initiator synthesis:

Diethyl peroxydicarbonate[2,3] (DEPDC) is synthesized by reacting 12 mL ethyl chloroformate with 6.64 mL 30% H_2O_2 and 24 mL 5M NaOH in 100 mL pre-cooled (0-5°C) demineralized water under stirring. The reactants are added in the given order drop by drop to ensure that the temperature never exceed 10°C. After stirring for another 10 min, 50 mL of pre-cooled (-18°C) hexane is added to extract DEPDC under increased stirring speed for 5 min. The mixture is transferred to a separation funnel and the organic phase is collected. The extraction and separation are done twice. Traces of water are removed by adding molecular sieves. The

produced DEPDC is stored in hexane with molecular sieves at -18°C. The concentration of DEPDC in hexane is measured to 0.2 M by titration with iodine.[4] The initiator mixture is regularly examined by semi-quantitative peroxide test stick Quantofix supplied by Macherey-Nagel (Germany). Iodine titrations showed that DEPDC is stable at -18°C for several months.

Sample preparation:
Injection moulded Silopren LSR2050 sheets (thickness: 2 mm) are supplied by Momentive Performance Materials (USA). The sheets are heat cured in an oven at 200°C for 4 hours and subsequently extracted in liquid CO_2 for 8 hours. The sheets are then cut into dumbbell shaped specimen using a die cutter ISO37 type 4 die (Elastocon AB, Sweden). Finally about 5 mm are cut from both ends of the specimen for a better fit in the reactor.

IPN production:
Experiments are run in series of four. For each experimental setting four numbered 16 mL stainless steel high-pressure reactors equipped with pressure transmitter, x-magnet and grid are applied. The reactors are placed in an oven at 120°C for at least two hours for removal of water, then the reactors are closed and allowed to return to ambient temperature. Then the reactors are loaded in succession with 0.5-4 mL HEMA, 1%mol EGDMA with regard to HEMA, 4.00 mL EtOH and three marked and weighed dumbbell specimen in the given order, then the reactor is placed in a 75°C preheated water bath, and the next reactor is loaded. When all reactors are loaded, they are pressurized in succession with CO_2 to approx. 260 bar at 75°C, each reactor is connected to the pump for about five minutes. When the last reactor is pressurized, 500 µL 0.2 M DEPDC in hexane solution and CO_2 is added to each reactor in succession by applying a HPLC injection loop to ensure a pressure of approx. 350 bar at 75°C, each reactor is connected to the pump for about three minutes. All experiments are polymerized over night. The experiment is terminated by slowly releasing the pressure over approx. 5 minutes. Then the specimen are cleaned in EtOH for removal of excess polymer material. Then they are placed in an oven at 50°C for two days for drying before they are weighed and the PHEMA content of the resulting IPNs is determined.

Water uptake:
The dried IPNs are placed in a dissicator for minimum 30 minutes then they are weighed and placed in individual vials containing demineralized water. At given times the IPNs are individually removed, wiped gently with lens paper to remove excess water and weighed. Then the IPN is returned to its vial.

Tensile testing:
Preliminary experiments have shown that the mechanical properties are dependent on the degree of swelling. Therefore the IPNs are placed in water for at least seven days prior to mechanical testing in order to obtain equilibrium swelling.

All tensile testing is performed on a Tinius Olsen H5KT equipped with a 1000 N loadcell. An IPN is removed from water and wiped gently with lens paper and the cross-section area is determined. The IPN is then placed in the grips on the Tinius Olsen equipment with a gauge

length of 20 mm and run with a test speed of 50 mm/min until breakage. The QMat 5.36 T-Series 5k software auto-detect the tensile strength and elongation at break.

RESULTS AND DISCUSSION

The PHEMA content in an IPN is given by equation (1).

$$\text{PHEMA content} = \frac{m_{\text{IPN}} - m_{\text{Silicone}}}{m_{\text{IPN}}} \cdot 100\% \tag{1}$$

The PHEMA content of the produced IPNs are listed in table \ref{tab:phemacontent}.

Table 1: PHEMA content in the produced IPNs. The A,B and C refers to the three dumbbell specimen in each reactor. On the left hand side of the table the amount of HEMA in the feed is listed for clarification.

V_{HEMA} (µL)	A (%wt)	B (%wt)	C (%wt)	V_{HEMA} (µL)	A (%wt)	B (%wt)	C (%wt)
500	-0.3	-0.4	-0.4	2000	19.0	19.3	19.6
	-0.3	-0.4	-0.2		23.4	23.7	22.2
	2.1	2.0	2.1		23.8	24.7	24.7
	3.1	2.7	2.8		26.2	25.0	24.8
1000	11.2	11.1	11.1	3000	22.0	19.8	20.4
	12.3	12.6	12.2		34.3	33.0	33.3
	12.6	13.2	13.1		29.4	29.3	29.8
	13.4	13.9	13.9		37.2	37.6	36.6
1500	15.9	15.9	15.4	4000	43.9	45.0	45.1
	17.5	16.9	16.4		38.5	38.0	36.0
	14.9	15.4	16.5		45.2	45.7	44.6
	20.4	19.5	21.3		43.0	42.1	40.5

Figure 2 shows the PHEMA content of the produced IPNs as function of the volume of HEMA in the feed. As can be seen from figure 2 the volume of HEMA in the feed has a clear influence on the PHEMA content in the resulting IPNs. The two dashed lines shows the 95% confidence interval. This means that if 2000 µL HEMA is added to the feed the resulting IPN in 95% of the experiments will have a PHEMA content between 18.2 and 26.8%. The 95% confidence interval is given by equation (2) and (3),

$$\text{PHEMA content} = 8.6190 \cdot V_{\text{HEMA}} + 1.0047 \tag{2}$$

$$\text{PHEMA content} = 11.2840 \cdot V_{\text{HEMA}} + 4.2287 \tag{3}$$

where PHEMA content is in unit \%wt and V_{HEMA} is the amount of HEMA added to the feed in mL.

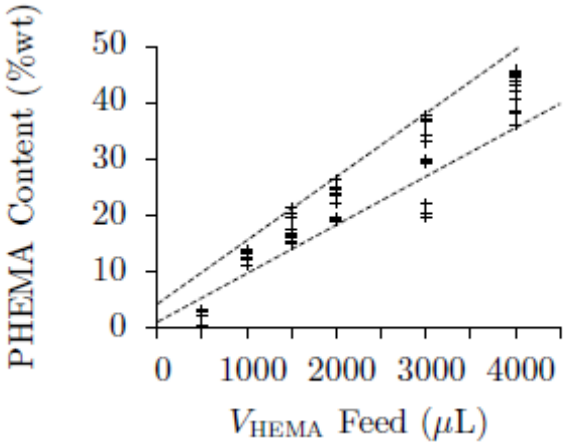

Figure 2: PHEMA content in the IPNs plotted against the volume of HEMA added to the reactor.

As can be seen from table 1 the PHEMA content of the three specimen within the same reactor generally is within 1%wt. This indicates that there have been homogenous reaction conditions within the reactors, i.e. there has been/are sufficient stirring when three dumbbells are added to the reactor. Table 1 reveals that there is a greater difference in the PHEMA content between the individual reactors than between the three dumbbells in one reactor, which might question the reproducibility. This tendency, however, might be explained by the small differences induced by the experimental setup, such as: pressure profile, temperature profile, impregnation time etc.

It is clear from table 1 that 500 µL HEMA in the feed is insufficient to obtain continues interpenetrating polymer networks. This is due to the too low concentration of HEMA. Some of the IPNs with 500 µL even loose weight during the experiments and the subsequent drying. This might be because the specimen are not dried before the experiments, and silicone is known to absorb about 3-5%wt moisture from the surroundings. Furthermore, non-vulcanized silicone oil might be extracted during the experiment, even though the samples are both heat cured and extracted in liquid CO_2.

Water uptake:
The water uptake of the IPNs are determined. The equilibrium water content (EWC) is given by equation (4).

$$\mathrm{EWC} = \frac{m(t) - m(0)}{m(t)} \cdot 100\% \tag{4}$$

where $m(t)$ is the mass of the IPN placed in water at time t, and $m(0)$ is the initial mass. Figure 3 shows the water uptake profile for a dumbbell that contains 23.7%wt PHEMA and has a typical profile.

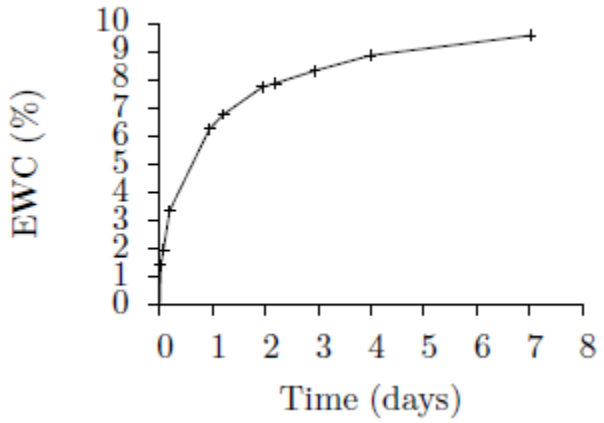

Figure 3: Typical water uptake profile for the produced IPNs. Dumbbell containing 23.7%wt PHEMA is used as an example.

Equilibrium swelling of the produced IPNs (thickness about 2 mm) is obtained after approximately one week, as is seen on figure 3. In figure 4 the equilibrium water content (EWC) after one week of all the produced IPNs is plotted against the PHEMA content.

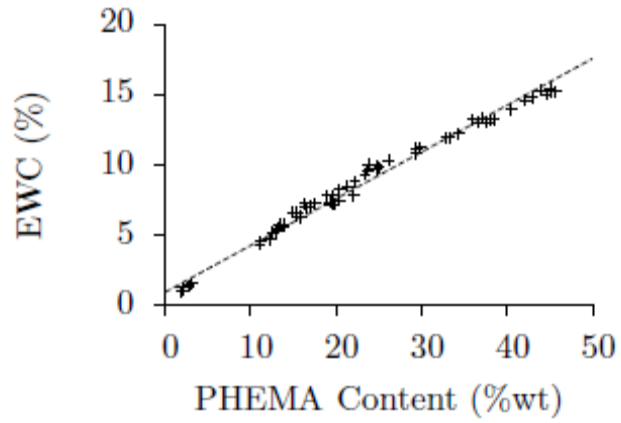

Figure 4: EWC of IPNs after they are soaked in water for approx. one week as function of PHEMA content in the IPNs.

As can be seen from figure 4 there seems to be a linear relationship between EWC and the PHEMA content. This suggests that all the impregnated PHEMA contributes to the water uptake and hence is surface connected. This is supported by figure 5 which contains the EWC of the PHEMA in the individual IPN as function of time for all the produced IPNs, a total of 60 IPNs.

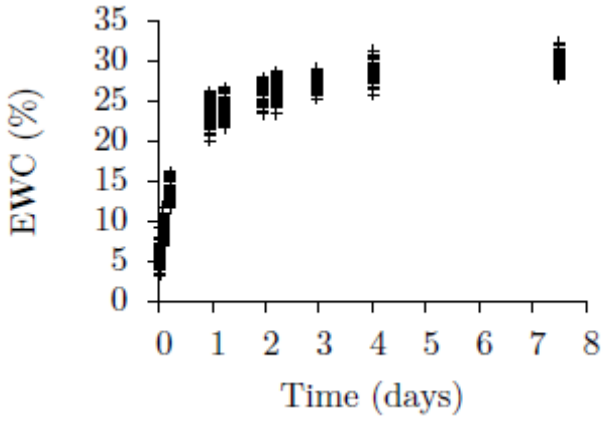

Figure 5: Water uptake profile for the produced IPNs, based on the relative PHEMA content instead of the IPN.

Tensile testing:

The tensile strength and elongation at break for the produced IPNs soaked in water for approx. a week as function of the PHEMA content is given in figure 6 and 7 respectively.

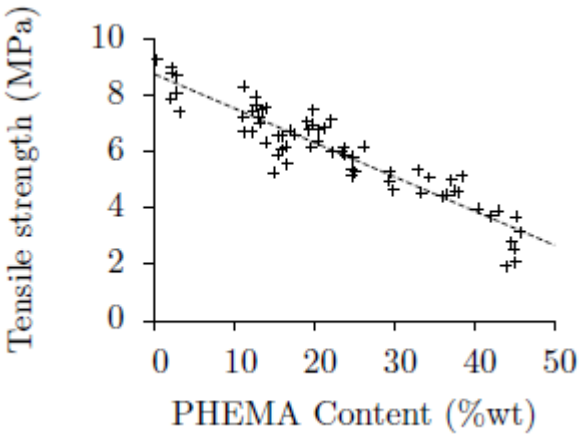

Figure 6: Tensile Strength of IPNs after they are soaked in water for approx. one week as function of PHEMA content in the IPNs.

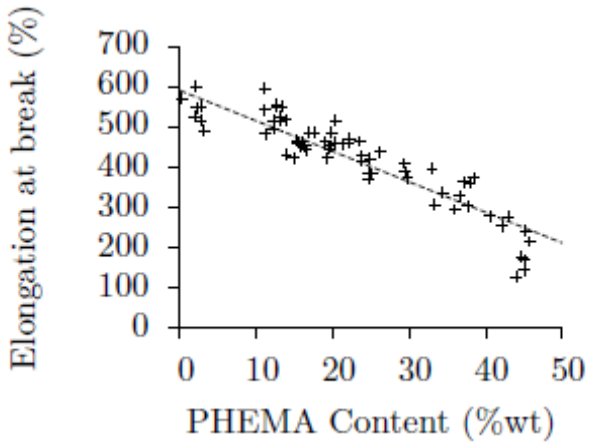

Figure 7: Elongation at break for the produced IPNs soaked in water for approx. a week as function of the PHEMA content.

Both the tensile strength and elongation at break seems to be linear dependent of the PHEMA content, cf. figure 6 and 7. Whether this arises from the fact that the matrix consist of two individual networks with different properties, such as concrete and steel composites, is not known. One possible explanation for this is that the PHEMA inside the IPN makes a pre-stress on silicone matrix. Meaning the silicone is still broken at the same stress and at the same elongation, but the offset is altered. Therefore the decreases in tensile stress and elongation at break are not a measure of the material becoming weaker but a measure of the applied pre-stress arising from the increased PHEMA content.

CONCLUSION

It has been shown that it is possible to produce interpenetrating polymer networks of silicone rubber and 2-hydroxyethyl methacrylate in supercritical carbon dioxide. The relationship between the concentration of monomer in the feed and the obtained hydrogel content in the IPN has been modeled. Furthermore the water uptake and mechanical properties of said IPNs have been described. It is apparent that there are a linear relationship between the hydrogel content and both the water uptake and the mechanical properties.

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