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Fabrication of non-dissolving analgesic suppositories using 3D printed moulds

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ABSTRACT

Conventional suppositories sometimes fail in exerting their therapeutic activity as the base materials melt inside body cavities. Also they are not suitable to provide long term treatment. Biomedical grade silicone elastomers may be used to fabricate non-dissolvable suppositories to overcome these disadvantages. We kneaded 4 analgesics into the 2 kinds of silicone polymers at 1%, 5% and 10% drug loading, respectively, to test their mechanical properties and drug release profiles. The optimized drug-polymer combinations were used to fabricate suppositories, and three dimensional printing (3DP) was used to create the suppository moulds. Subsequently, the drug release profiles and biocompatibility of the suppositories were studied. It was found that, the mechanical properties of the drug laden silicone elastomers and the rate of drug release from the elastomers can be tuned by varying drug-polymer combinations. The silicone elastomers containing 1% (w/w) and 5% (w/w) diclofenac sodium were the optimal formulations with prolonged drug release and biocompatibility at cellular level. These properties, together with complex geometries offered by 3DP technique, potentially made the non-dissolving suppositories promising therapeutic agents for personalized medicine.

1. Introduction

Suppositories are dosage forms intended for rectal, vaginal and urethral applications, to exert local or systemic effect (Leon Shargel, 2010). They are useful for children, the severely debilitated and those with difficulty taking conventional medications. The suppository base materials can be hydrophobic, hydrophilic and amphiphilic (Yarnykh et al., 2011). These materials melt at body temperature to release drugs to the site of application. The melted suppository debris may migrate up or leak out of the location of administration, and fail to achieve their therapeutic effect (Peppas et al., 2000). Besides, extended drug release is not possible by using these melting base materials.

To this end, silicone elastomers may be a suitable alternative as suppository bases, owing to their biocompatibility and non-biodegradability (Říhová, 1996). These elastic materials can provide snug fit for clinical applications. The non-biodegradable materials can potentially prevent the suppository from melting and/or displacement inside human cavities. On the other hand, these elastomers can also be used to deliver drugs (Baum et al., 2012; Fu and Kao, 2010) sustainably for long-term treatment.

Long term analgesic treatment with suppository is needed for patients who suffer from postpartum perineal pain, post-operative pain of gastrointestinal surgery and terminally ill cancer pain (Ali Ebrahim et al., 2014; Andrews et al., 2008; Davis et al., 2002; Dodd et al., 2004; Kirchhoff et al., 2010; Lowenstein et al., 2006; Macarthur and Macarthur, 2004; Petrowsky et al., 2004; Yoong et al., 1997; Wilasrusmee et al., 2008). For these patients, oral delivery of painkillers for long term treatment is either challenging or prohibitive, therefore, non-dissolvable analgesic suppositories can provide a useful alternative treatment option.

The commenly used painkillers include lidocaine hydrochloride (LidoHCl) and non-steroidal anti-inflammatory agents (NSAIDs). The sodium salt forms of diclofenac and ibuprofen have been used in suppositories (Davis et al., 2002; James Barron, 1977; Rezaei et al., 2014). Different from diclofenac and ibuprofen, the free acid

Abbreviations: Diclo, diclofenac sodium; Ibu, ibuprofen sodium; Keto, ketoprofen; LidoHCl, lidocaine hydrochloride monohydrate; NSAIDs, non-steroidal anti-inflammatory dugs; PBS, phosphate buffered saline; 3DP, three dimensional printing.

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form of ketoprofen is often used in the clinical applications, rather than its sodium salts (Souza et al., 2013).

In this study, we investigate the interaction of drugs of different physicochemical properties and polymers of varying chain lengths. The mechanical properties of these drug laden elastomers and the drug release from the elastomers were studied. Subsequently, non-dissolvable suppositories have been developed by using the elastomers. The suppository moulds were fabricated by using three dimensional printing (3DP). The novel approach can be used to fabricate suppository moulds of various shapes and sizes to meet the requirements of physicians and patients, potentially useful for personalized medicine (Goyanes et al., 2015).

2. Materials and methods

2.1. Cells

The cells used for the cytotoxicity testing were L-929 mouse fibroblast (ATCC® CCL-1™). The cells were cultured in T-75 flasks at 37 °C, in an atmosphere of 5% CO_2, and subcultured twice a week. The culture medium was Dulbecco's modified Eagle's medium (DMEM) (Gibco® by life technology™, USA) supplemented with 10% (v/v) fetal bovine serum (FBS) and 1% (v/v) of 10,000 unit/ml penicillin and 10,000 μg/ml streptomycin. Adherent cells were detached with a mixture of 0.025% trypsin (Gibco® by life technology™, USA) and 0.02% ethylenediaminetetraacetic acid (EDTA), incubated for 7 min at 37 °C and used for cell inoculation.

2.2. Materials

Drug laden elastomers were fabricated by using Silastic® Q7-4720 (Dow Corning, USA) and MED-4901 (NuSil, USA) silicone polymers. Both polymers were supplied as two-component kits. Part A contained the platinum catalyst and part B contained the cross-linkers. The part A to B ratio was 10:1 for Silastic Q7-4720 and 1:1 for MED-4901. Diclofenac sodium (Diclo) (CAS No.: 15307-79-6), Ibuprofen sodium (Ibu) (CAS No.: 31121-93-4), Lidocaine hydrochloride (LidoHCl) (CAS No.: 6108-05-0) and Ketoprofen (Keto) (CAS No.: 22071-15-4) were supplied by Sigma-Aldrich (USA). 3DM Castable resin (Kudo3D Inc., USA) was used to fabricate the suppository moulds. All the materials were used as supplied without further purification.

2.3. Fabrication process for elastomer-drug interaction testing

For drug-laden elastomers, drugs and silicone polymers were kneaded together and pushed into (using a syringe) cylindrical polypropylene mould (diameter = 2.8 mm) for preliminary test. These polymers were then cured for 18 h at 70 °C (Silastic elastomers) and 60 °C (MED-4901 elastomers) (Fig. 1). Drug distribution within the elastomers were characterized using a SMZ1500 stereo microscope (Nikon, Japan).

The suppository moulds were designed and created with AutoCAD© 2016 (San Rafael, USA) (Fig. 2). Then the computer-aided design (CAD) model was sliced into 100 μm horizontal layer images by a slicing algorithm using the software Creation Workshop (DataTree3D Inc., USA), the images were compressed into a zip file and loaded onto Titan1's control software (Kudo3D Inc., USA). The sliced layers were built up with 3DM Castable resin by the printer (Titan 1, Kudo3D Inc., USA) to create the three dimensional moulds layer by layer. The moulds were rinsed with Isopropyl Alcohol (IPA) with agitation for 15 min before being subjected to UV light for 2 h for post processing.

2.4. Mechanical tests

The drug-laden elastomers were first sectioned to 40 mm length, and 20 mm were marked in the middle of the sample with non-destructive ink. Precise measurement of the length was taken (L_0) to calculate the strain. The diameters of the section were taken at three different points using a vernier caliper to calculate an average cross-section area for stress calculations. Specimens were clamped at each end up to demarcated margins using Instron 5500 Series Material Testing System and tested at 50 mm/min crosshead velocity.

Tensile stress is defined as the load on the specimen per unit area:

$$\textit{Tensile stress} = \textit{load}/(\textit{cross-sectional area}) \quad (1)$$

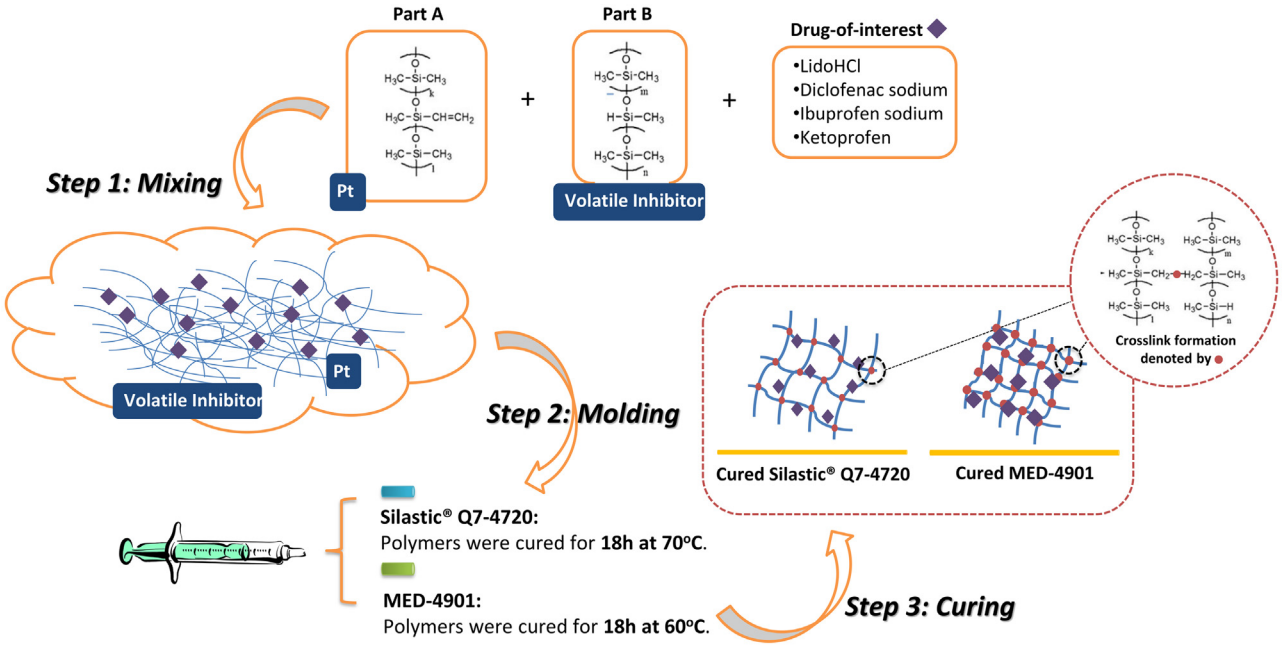

Fig. 1. Schematic representation of the curing process of silicone elastomers.

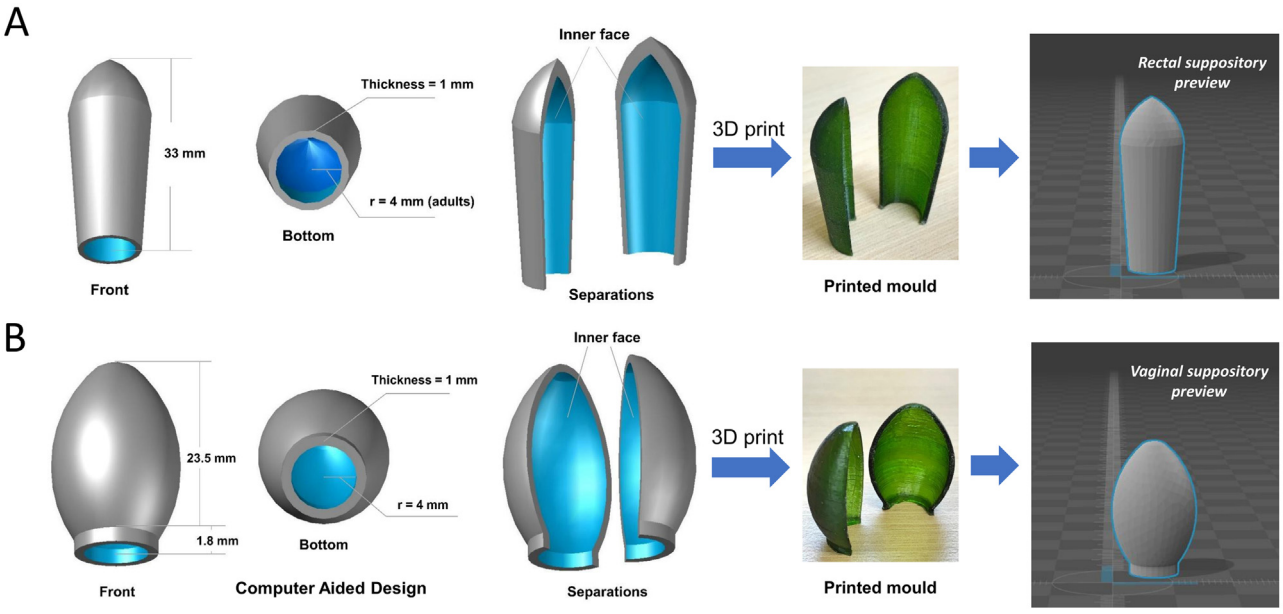

Fig. 2. The computer aided design of suppository moulds for (A) rectal suppository and (B) vaginal suppository for 3D printing.

Strain measures the change in gauge length relative to the original gauge length:

$$Strain = (L - L_0)/L_0 \quad (2)$$

Young's modulus is calculated from the gradient of the initial linear portion of the stress-strain curve. It measures the stiffness and elasticity.

The ability of the materials to withstand plastic deformation was analyzed through their *residual elongations*. A higher residual elongation indicates the reduced ability of the elastomer to return back to its original shape after stretching. To measure residual elongation, the specimen of sample was sectioned and held between two clips. Then, the sample was stretched, at an even rate, to a length three times that of the original. The specimen was held for 10 min in the elongated state and allowed to rest for 10 min thereafter. At the end of the 10 min resting period, the distance was measured again between the bench marks. Residual elongation is calculated as:

$$E = (L - L_0)/L_0 \quad (3)$$

E is the elongation in percentage;L is the observed distance between bench marks after the 10 min' rest (mm);L_0 is the original distance between bench marks (mm).

2.5. In vitro *release study*

The drug release profiles of drug-laden elastomers were tested *in vitro* using phosphate-buffered saline (PBS) at 37 °C. Each sample (0.2 g) was placed in Falcon tube containing 10 mL of phosphate buffered saline (PBS) (pH 7.4), except ketoprofen laden samples which were placed in Falcon tubes containing 50 mL of PBS to maintain sink conditions. At designated time points, samples were removed from the falcon tubes and the release test solutions were entirely replaced with fresh ones. Samples of the release test solutions were analyzed using an ultraviolet spectrophotometer (Hitachi U-1900, Japan) at wavelengths 216.5 nm (LidoHCl), 276 nm (diclofenac sodium), 259 nm (ketoprofen) and 221 nm (ibuprofen sodium) to determine the concentrations of the various compounds released. Standard calibration curves were prepared using drugs at varying concentrations within the linear portion of the absorbance-concentration curve. To offset the presence of any degradation products within the silicone elastomers that may affect the spectrophotometric determination, blank silicone bands were prepared as negative controls. All release studies were done in triplicates. The UV absorbance spectrums of release samples from the blank and drug-laden polymers were also characterized and compared against the reference drug at designated time points to confirm that the release sample solutions contained the drug-of-interest, with minimal interference from the polymer added at the wavelengths of interest.

2.6. Suppository fabrication and release test

Based on the preliminary studies, the optimal formulations were chosen to fabricate suppositories. Polymers with drug were smeared into 3D printing moulds. After curing, the suppositories were retrieved from the moulds. The suppositories were weighed (w grams) and placed in falcon tubes, w/0.2 mL PBS was added to mimic the physiological conditions, according to BS EN ISO-19003-12:2012 (BSI, 2012). At each time point, PBS was collected and filtered with 0.2 μm microporous membrane filters, and fresh PBS was added. To quantify the amount of released drug in the suppositories accurately, UPLC analysis was used. The UPLC system comprised of a Shimadzu UPLC system (Shimadzu, Kyoto, Japan), using a LC-20AD pump, SIL-20A HT auto sampler, CTO-20A column oven and SPD-20A UV/VIS detector. The column was ACE C18 (4.6 mm × 250 mm, 5 μm, Advanced Chromatography Technologies Ltd, Scotland). For LidoHCl, the mobile phase was 70% (v/v) of acetic acid (pH adjusted to 3.4) and 30% of pure acetonitrile, at the wavelength of 254 nm; for diclofenac sodium, the mobile phase was 60% (v/v) of 10 mM potassium dihydrogen phosphate (pH adjusted to 6.3) and 40% of pure acetonitrile, at the wavelength of 276 nm. Analyses were carried out at a flow rate of 1.5 mL/min and the injection volume was 20 μL. All tests were done in triplicates.

2.7. Cytotoxicity testing

The suppositories were incubated with PBS at 37 °C for 24 h. The extracting solutions were then filtered through 0.2 μm microporous membrane filters. L-929 cell suspension was prepared at a concentration of 1.67×10^4 cells mL^{-1} and inoculated onto 96-well plates (180 μL per well). The plates were incubated at 37 °C, 5% CO_2

for 24 h. 20 μL of extract were pipetted into seeded wells, these wells served as the experimental wells. 20 μL of sterile PBS were added onto remaining seeded wells, which served as the controls. Then, 20 μL of sterile PBS were pipetted in unseeded wells, which served as blank. The cells were incubated at the same conditions stated above for up to 5 days. 22 μL of PrestoBlue™ Viability Reagent (Thermo Fisher Scientific Inc., USA) was pipetted into testing wells. The 96-well plates were then incubated for 30 min at 37 °C, 5% CO_2. Subsequently, the absorbance was analyzed with SpectraMax® 190 absorbance microplate reader (Molecular Devices, LLC., USA) at the wavelength of 570 nm with a reference wavelength of 600 nm.

2.8. Statistical analysis

All analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corporation, USA) and OriginPro 2016 (OriginLab Corporation, USA). Both non parametric and parametric tests were used. A p-value of less than 0.05 was considered significant.

3. Results

LidoHCl crystals existed as translucent drug crystals embedded within the polydimethylsiloxane matrix (Fig. 3A). Diclofenac sodium, ibuprofen sodium and ketoprofen were present as spherical white particles uniformly dispersed within the polymer (Fig. 3B–D).

For Silastic, the stiffness and elasticity decreased when increasing drug loading of LidoHCl, while they remained comparable among the NSAIDs except ibuprofen sodium (Fig. 4A). No significant difference in stiffness was observed in MED-4901 elastomer at various drug loadings (Fig. 4A). Data from Ketoprofen laden MED-4901 polymers were excluded due to insufficient curing. Compared to drug laden Silastic elastomers, MED-4901 drug laden elastomers showed lower and more stable stiffness.

A reduction in the ability to withstand plastic deformation (reflected by the values of residual elongation) were observed at increased LidoHCl laden Silastic elastomers (Fig. 4B). Similarly, the addition of increasing concentrations of diclofenac sodium, ibuprofen sodium and ketoprofen also adversely affected the mechanical properties Silastic elastomers in terms of the ability to tolerate deformation (Fig. 4B). MED-4901 elastomers were better able to resist plastic deformation compared to Silastic elastomers regardless of the concentration of LidoHCl, diclofenac sodium and ibuprofen sodium added ($p < 0.05$) (Fig. 4B).

At 1%, 5% and 10% drug loading in Silastic elastomers, ketoprofen showed the fastest initial release, followed by LidoHCl, ibuprofen sodium and diclofenac sodium (Fig. 5A). LidoHCl plateaued the earliest among the four drugs, within 19 h for both 1% and 5% drug loading and 10 days for 10% drug loading in Silastic polymers. During the 30-day drug release study, ketoprofen laden Silastic polymers released the most drug, followed by ibuprofen sodium, LidoHCl and lastly diclofenac sodium at 5% and 10% drug loading. Among MED-4901 polymers, LidoHCl showed the fastest initial release at 1%, 5% and 10% drug loading, followed by ibuprofen sodium and diclofenac sodium (Fig. 5B). LidoHCl release plateaued at 19 h for 1%, 2 days for 5% and 10 days for 10% drug loading. Between the three drugs tested, the cumulative release in MED-4901 elastomer was the highest for ibuprofen sodium, followed by diclofenac sodium and lastly LidoHCl at 1% and 5% drug loading.

MED-4901 loaded with 1%, 5% LidoHCl and diclofenac sodium were selected for suppository fabrication. At 1% and 5%, LidoHCl and diclofenac sodium suppositories were loaded with 60 mg and 300 mg of drugs, respectively. The initial release rate of LidoHCl and diclofenac sodium showed no difference ($p > 0.05$). Both 1% LidoHCl and diclofenac sodium suppositories released about 6.5 mg of loaded drugs, and 8.8 mg for 5% within 3 h. The suppositories containing 1% and 5% LidoHCl plateaued after releasing for 4 days, with the total amount of released LidoHCl being 9.20 ± 0.16 mg and 14.25 ± 0.44 mg. For 1% diclofenac sodium suppository, cumulative release for up to 96% was observed in 30 days, which was 57.35 ± 0.50 mg of diclofenac sodium; 5% diclofenac sodium suppository released 96.18 ± 1.30 mg of drug (Fig. 6).

In the cytotoxicity testing, exposure of L-929 cells to 5% LidoHCl or diclofenac sodium suppositories extracts did not affect the cell survival rates in 5 days. No significant difference was found between control group and experiment group ($p > 0.05$) (Fig. 7).

4. Discussion

Silicone polymers can be cured by two methods, namely, peroxide curing or platinum-catalyzed addition reactions. Both silicone polymers used in our study were cured by addition reactions. Polymers which utilized peroxide curing were not chosen since peroxide radicals may interact with the drug moieties and degrade them during the curing process (de Buyl, 2001). Despite the inert nature of our chosen silicone polymers, incorporating drugs within the silicone matrix was challenging as the platinum catalyst may be 'poisoned' by compounds containing amine, tin, sulphur and carboxylic acid groups (Snorradottir et al., 2009). Ketoprofen laden MED-4901 elastomers were unable to be completely cured in our study, possibly due to the presence of such groups *i.e.*, COOH, and this character may also cause the insufficient curing of ketoprofen laden Silastic, which finally led to a high release of ketoprofen.

To incorporate the drugs into the elastomer, a possible solution is to use its salt forms. Sodium salt was chosen in our study because it showed a higher degree of cure compared to the potassium salt in ibuprofen laden polymers (Snorradottir et al., 2009). Diclofenac sodium, despite holding a secondary amine group, this drug laden polymers were able to be cured, possibly one was due to the sodium salt composition, the other was because the formation of intra-molecular hydrogen bonds between the carboxylate group of diclofenac sodium and the secondary amine, which prevented the –NH moiety from forming inter-molecular hydrogen bonds with the siloxane backbone.

For Silastic elastomers, drug loading decreased the ability of resisting plastic deformation. This may be associated with an increase in the number of drug particles disrupting the ordered cross-links found within this polymer (Li et al., 2011). To this end, MED-4901 polymer was superior to Silastic polymer as suppository material, considering its ability to resist plastic deformation regardless of the types of drugs and their concentrations. At the same time, the pliable MED-4901 elastomers may offer a more comfortable fit for the patients as the suppository base.

From the release profiles of drug-laden elastomers, it seems that the release of drugs correlated with the permeability of the silicone elastomer (Raul et al., 2006). Given the porous nature of these polymers and the molding method, drugs of smaller particle size were able to diffuse out from the micro-channels present with less resistance (Golomb et al., 1990). We noted that ketoprofen elastomers released the most drug during the 30-day release studies, followed by ibuprofen sodium and diclofenac sodium. This trend correlated with the diameter of the drug particles, which were 6.67 μm, 10.00 μm and 13.33 μm for ketoprofen, ibuprofen sodium and diclofenac sodium, respectively.

Interestingly, LidoHCl showed higher initial release than diclofenac sodium despite having a much larger particle size of

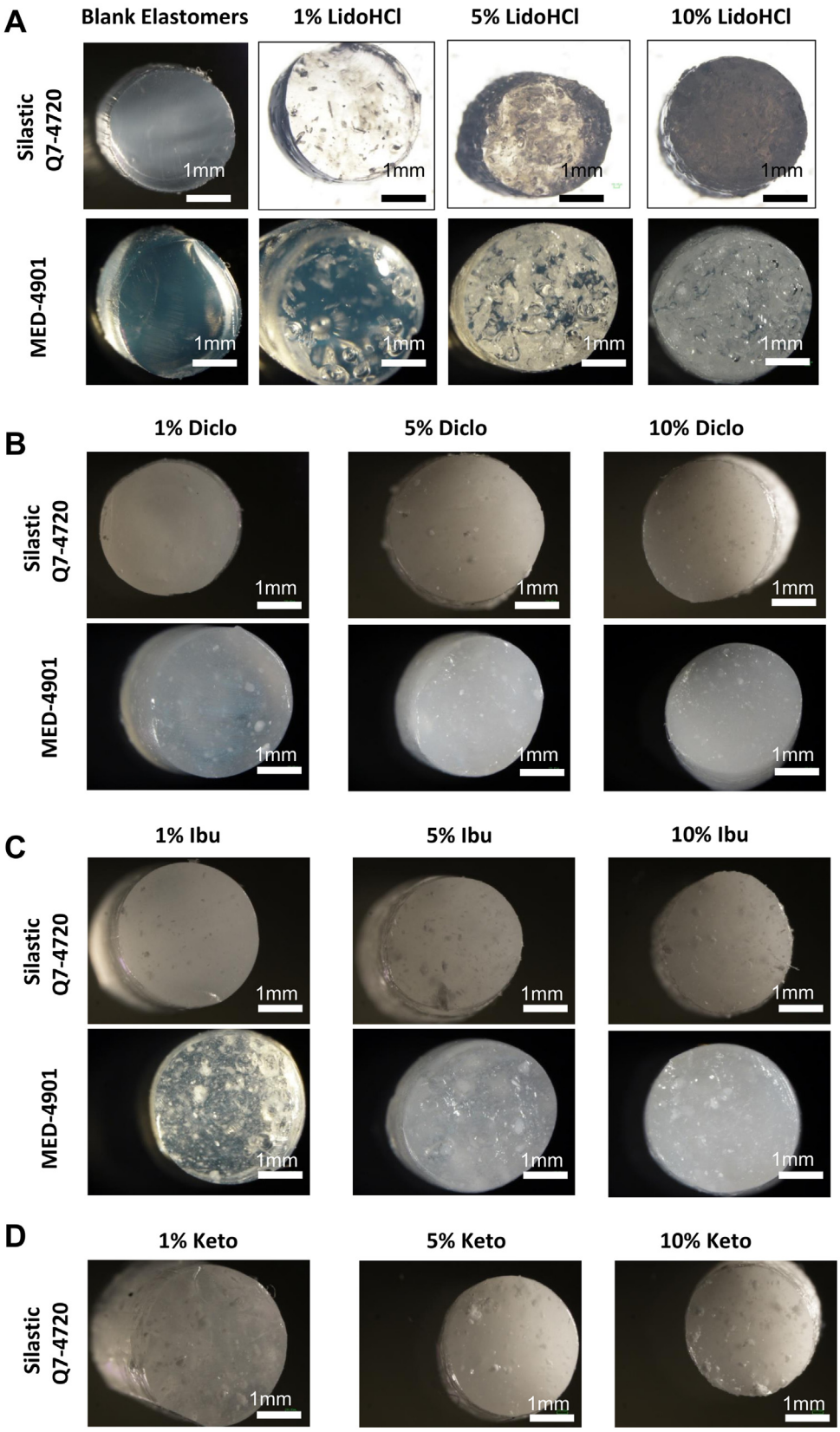

Fig. 3. Cross section of cured drug laden silicone elastomers. Percentages indicate% loading of various drugs within the silicone polymers.

150 μm. This could be due to the high solubility of LidoHCl in PBS (508.76 mg/ml) compared to diclofenac sodium (8.21 mg/ml). Given the propensity of LidoHCl to dissolve in PBS, the dissolution of peripheral LidoHCl molecules created empty pores from which PBS can enter, further solvating LidoHCl particles trapped deep within the convoluted micro-channels of the silicone polymer

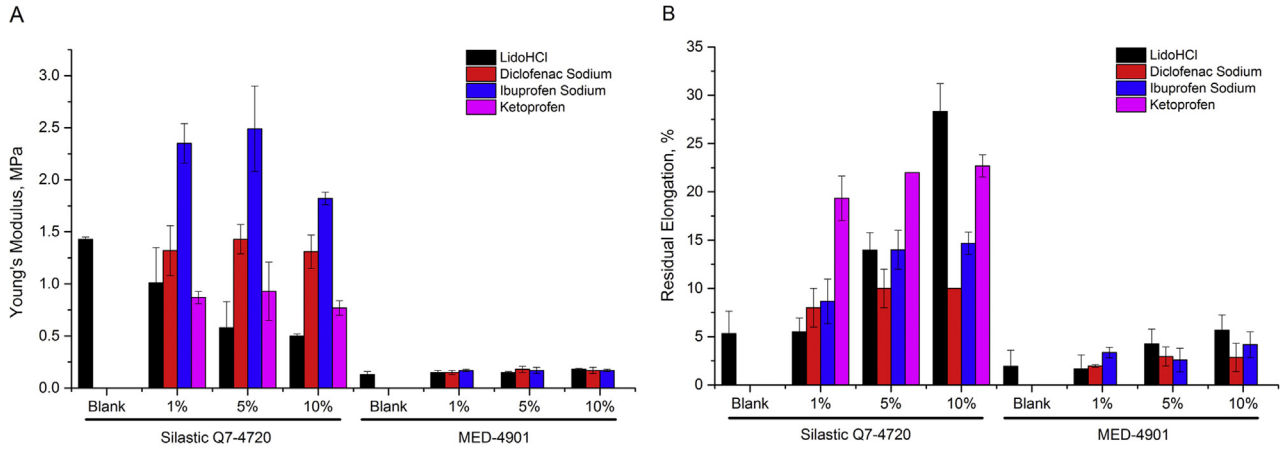

Fig. 4. Comparison of mechanical properties between Silastic and MED-4901 polymers laden with different drugs at 1%, 5% and 10% drug loading (A) Young's Modulus and (B) residual elongation.

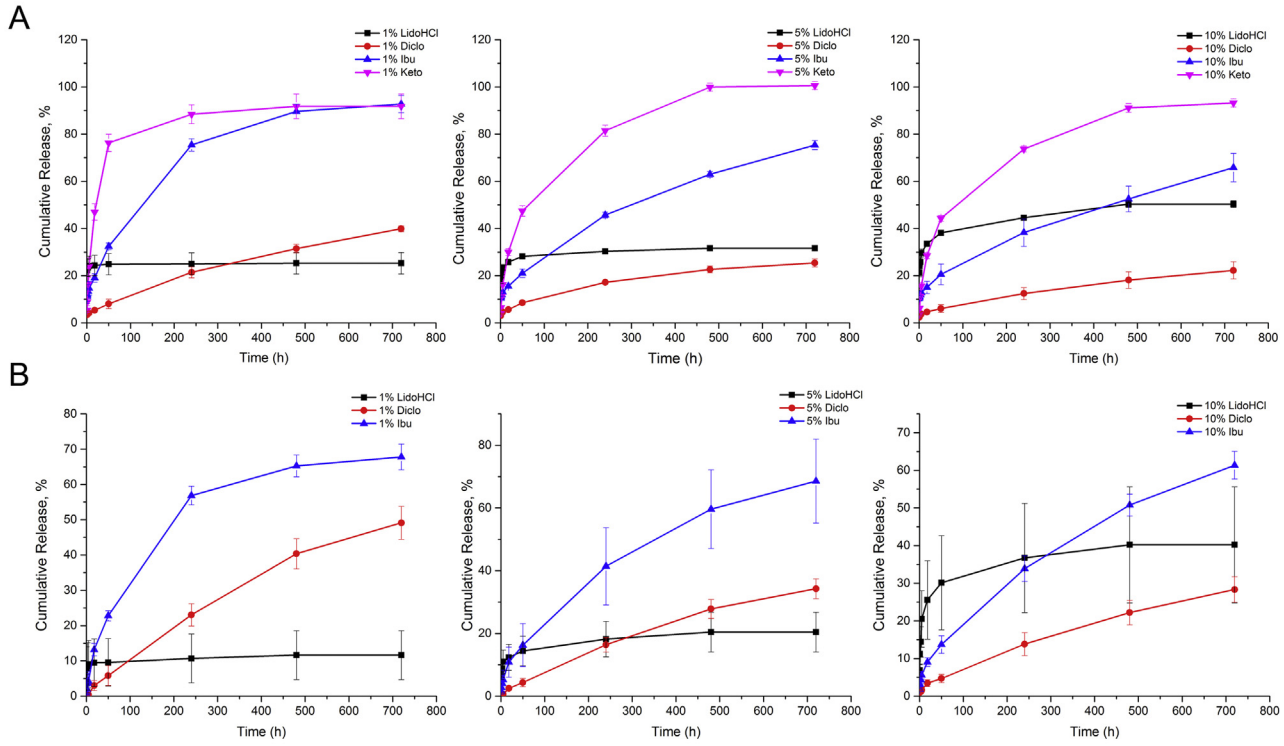

Fig. 5. Cumulative release of 1%, 5% and 10% diclofenac sodium (Diclo), ibuprofen sodium (Ibu), ketoprofen (Keto) and LidoHCl from (A) Silastic and (B) MED-4901 elastomers.

(Snorradottir et al., 2009). Once LidoHCl crystals were solvated, pore size no longer presents as a limiting factor to drug release.

Considering the drug-elastomer testing results, MED-4901 were used for suppository fabrication, but not Silastic (Table 1). In terms of drug selection, LidoHCl, ibuprofen sodium and diclofenac sodium did not cause significant changes of the cured MED-4901 elastomers. LidoHCl laden elastomers have fast onset of drug release, hence useful for immediate pain-relief. Clinically, the excretion of diclofenac in human milk has been reported low, which is comparatively safer during breast-breeding for postpartum women with perineum pain (Rezaei et al., 2014). Moreover, due to the prolonged release profiles of diclofenac sodium from the elastomers, it can be useful for the treatment of patients who suffer from long term terminally ill cancer pain. It's worth mentioning that high concentrations of drugs (≥10%) rendered viscous surfaces of suppositories by moulding method. Therefore, only 1% and 5% of LidoHCl and diclofenac sodium were used to fabricate the suppositories for subsequent testing.

The initial drug release profiles of LidoHCl suppositories and diclofenac suppositories were very similar. For diclofenac sodium suppositories, the cumulative release of drugs increased than that in the preliminary testing. It could have been caused by the different fabrication processes. In the preliminary testing, the polymers were squeezed with syringes and likely formed dense structures. In contrast, suppositories were fabricated without syringe extrusion, which may lead to larger pore sizes inside the elastomers, letting more diclofenac sodium diffusing out.

Compared with conventional suppositories, the ones we fabricated with bio-grade polymers will not melt at body temperature and have the ability of resisting plastic deformation

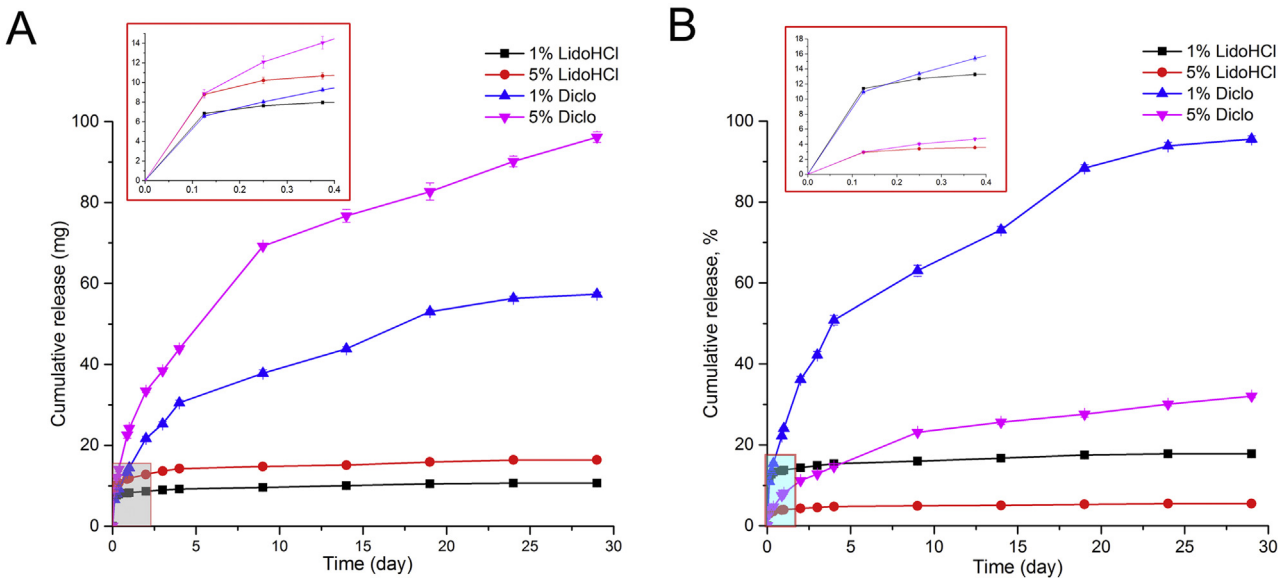

Fig. 6. Drug release profiles from MED-4901 suppositories with 1%, 5% LidoHCl and diclofenac sodium (A) cumulative drug release amount (mg) and (B) release percentage.

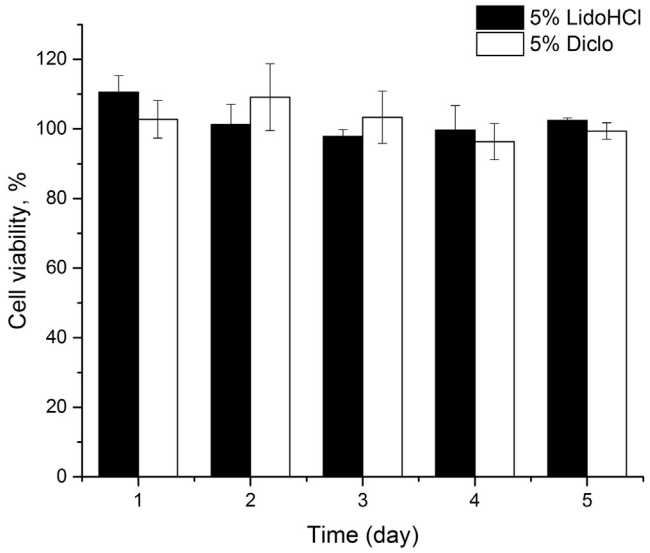

Fig. 7. Cytotoxicity testing of the suppository aqueous extracts.

inside body cavities. These characters allow the suppositories to stay at site of administration to exert its therapeutic activity. In addition, it can be retrieved easily by pulling a thread affixed to the suppositories to discontinue the medication (James Barron, 1977).

For current clinical practice, the suppositories of diclofenac are available in high dose and administered several times daily because of high protein binding (Setoguchi et al., 2013). The drug content has been reported to be 60 mg for lidocaine suppositories (Goluza et al., 2011) and 100 mg for diclofenac sodium suppositories (Lua et al., 2015). Azechi Y. et al. have reported two-fold longer half-life when controlled release suppository was administered (Azechi et al., 2000). Schneeweis, A. et al. have also reported the increase in mean residence time by controlling the release rate of the diclofenac (Schneeweis and Muller-Goymann, 1997). Therefore, the use of suppository providing the prolonged release will improve the therapeutic effect.

In this study, we tested 60 mg (1%) and 300 mg (5%) for both drugs, aimed at prolonged release to minimize the potential side effects (Irwin et al., 1995) and to reduce the dosing frequency. For vaginal administration these suppositories may provide prolonged therapeutic effects for up to a few weeks potentially.

Three dimensional printing, which emerges as a powerful tool in fabricating drug delivery systems recently, has been used as the method to fabricate suppository moulds in our study (Bandyopadhyay et al., 2015; Jonathan and Karim, 2016). The geometrical features were designed according to the shapes and sizes of human body cavities. This can be useful especially for women suffering from different degrees of vaginal relaxation syndrome or posterior prolapse (exacerbated by childbirth, especially multiple pregnancies and deliveries, and the vaginal atrophy). In this condition, muscles ligaments and fascia that hold and support the vagina become stretched and weakened. Thus, the appearance and size of the vaginal opening can vary, demanding customized vaginal suppositories (Goodman et al., 2010; Kegel, 1956; Lee, 2014). It has been reported that women had their own preference over the shape, size and firmness of the vaginal suppositories (Li et al.,

Table 1
Comparison of the drug laden elastomers in terms of mechanical properties and drug release.

Drugs	[a]Young's modulus, MPa		[b]Residual elongation, %		Releasing period, days	
	Silastic	MED	Silastic	MED	Silastic	MED
LidoHCl	>0.5	<0.25	>5	<0.25	<10	<10
Diclo	>1.25	<0.25	>7	<0.25	>30	≫30
Ibu	>1.75	<0.25	>7	<0.25	>30	≫30
Keto	>0.75	–	>15	–	<20	–

[a] Young's modulus represents the stiffness and elasticity.
[b] Higher residual elongation indicates the reduced ability of elastomer to return back to its original shape.

2013). Therefore, customized elastic vaginal suppositories made by 3DP could meet the needs of female patients, for instance, to fit in the cavities firmly to prevent migration and to offer acceptable sensory owing to the elastic nature of the materials.

Admittedly, 3DP is not confined to build the moulds of suppository. The pressure-assisted micro-syringes printing, one of 3DP methods, is a promising way to create complex drug delivery systems, potentially useful to fabricate elastic suppository directly (Khaled et al., 2014). This technology is based on extruding a viscous semi-liquid material from syringe to achieve a desirable 3D shape (Chia and Wu, 2015). However, extensive studies are needed to investigate the rheological properties of inks, the material stability and the drying process associated with this approach (Aho et al., 2015; Goyanes et al., 2015; Yu et al., 2007).

5. Conclusion

The mechanical properties of the drug laden silicone elastomers and the rate of drug release from the elastomers are tunable. MED-4901 is a promising base material to make non-dissolvable suppository for sustained drug release. In addition, 3DP is potentially useful in making personalized suppository moulds to meet the requirements and preferences of physicians and patients.

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