The stability of insulin solutions in syringes is improved by ensuring lower molecular weight silicone lubricants are absent

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Abstract

Protein drugs such as insulin are almost universally delivered via glass syringes lubricated with silicone oil. It is not uncommon for prefilled syringes (PFS) to become cloudy, which may affect bioavailability or total drug dose. To examine the role, if any, of the silicone oil lubricant in this process, a systematic evaluation of the degree of insulin denaturation and aggregation as a function of silicone oils of different molecular weights was undertaken. The former was measured using fluorescence changes of aqueous insulin/silicone dispersions, while the latter examined changes in turbidity as a function of mixing and silicone oil type; the results were confirmed at two different insulin concentrations and agitation speeds. Lower molecular weight silicones led to the most rapid denaturation and aggregation, and when examined in blends of silicones at a fixed viscosity of 1000 cSt, commonly used for syringe lubrication, more rapid denaturation/aggregation was noted in blends of silicones containing the largest fractions of low molecular weight materials. As a consequence, the molecular weight profile of silicone lubricants should be established prior to the preparation of prefilled syringes.
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1. Introduction

Prefilled syringes (PFS) of therapeutic proteins, such as insulin, are a rapidly growing and more advantageous mode of drug delivery than their syringe and vial predecessors [1, 2, 3]. According to a report by Smithers Rapra, the global market for PFS is expected to grow from $3 billion in 2013 to $6.6 billion by 2020, which will translate to the production of 6.7 billion PFS units that year [4]. This is unsurprising; a study conducted in a private Indian market found that the mean vaccination time and handling errors associated with PFS was twice as fast and three times fewer than the syringe and vial format, respectively [5]. In fact, PFS are generally considered more convenient, accurate and cost-effective [2]. Hence, given the need for dosage accuracy, and the high commercial demand, it is important for PFS manufacturers to ensure good mechanical performance of their units.

Smooth barrel gliding is one aspect of syringe performance that must be optimal; a balance must be struck between motion and resistance, and the initial inertia of the barrel to movement. To this end, lubricity in glass syringes is generally achieved using medical grade silicone oil, typically a polydimethylsiloxane (PDMS, Me₂Si(OSiMe₂)nOSiMe₃), n~ 380, 1000 cSt viscosity). This material provides the correct viscosity and shear-thinning properties [6, 7, 8, 9] while forming an excellent, biocompatible seal for the aqueous solution [10].

While silicone-lubricated PFS are generally advantageous, solution cloudiness has been observed in such syringes after several months of storage [11]; the situation is exacerbated by swings in temperature or induced agitation from shipping and handling [12, 13]. The cloudiness, which likely results from the aggregation of therapeutics, has been reported for different proteins after exposure to silicones, including the protein Orencia [14], monoclonal antibodies, fibrinogen, fibronectin, α-chymotrypsin, alkaline phosphatase and glucose oxidase [11, 15, 16, 17, 18]. It is believed that hydrophobes (like silicones) cause conformational changes in proteins that can expose their previously buried hydrophobic residues [19, 20]. The resulting hydrophobic interactions between hydrophobe and residues may keep the protein in a denatured, non-functional state, or be the precursor to aggregation or other unwanted outcomes.

Such protein stability issues may be addressed by optimizing the formulation of protein solutions. The use of surfactants like Polysorbate 20 [16], for example, reduces protein aggregation. Salt, by contrast, is affiliated with decreased emulsion stability and increased protein aggregation, as shown with lysozyme dispersions [21, 22]. But even with the advent of these strategies, some cloudiness can remain.
In the case of insulin filled syringes, patients sometimes notice cloudiness in samples that should normally be transparent [23]. Similarly, patients using lubricated syringes to draw insulin from vials have complained of abnormal glucose levels after taking their prescribed doses. As with other therapeutic proteins, the turbidity of insulin solutions has been linked to contact with silicones [24]. It is well understood, including by manufacturers [25, 26, 27, 28] that the first step in veil formation is the adsorption of proteins at the interface of dispersed silicone oil droplets, which is followed by protein unfolding (denaturation) [29]. This leads to the aggregation of denatured proteins [29]. The same phenomenon has been observed in silicone lubricated or treated glass and plastic syringes, cartridges, packaging and tubing that deliver or store protein therapeutics [11, 14, 30]. In fact, insulin has a strong propensity to aggregate in the presence of hydrophobic surfaces [31, 32], hence, the hydrophobic character of silicones is thought to facilitate the initial adsorption and unfolding.

To date, a systematic study comparing the effect of silicone oil types and molecular weight polydispersities on insulin has not been conducted. The latter is an important variable since silicone polymers are often sold as complex mixtures of materials; in general, the preparation of monodisperse silicones is very difficult [33]. Hence, most silicone fluids of a given viscosity are a broad mixture (approximately a Gaussian distribution) of structurally analogous materials of different molecular weights. We hypothesize that lower molecular weight silicones with lower viscosity are more effective at facilitating insulin denaturation and aggregation, as has been reported for the surface active protein, human serum albumin [34]. Given the well-documented utility of silicones as syringe lubricants [35] the effect of diverse silicones on insulin (as a model for other therapeutic drugs) requires further investigation. Agitation was used to accelerate the mixing outcomes of insulin with silicone oils of different molecular weights and polydispersities, and the extent of insulin denaturation and aggregation was measured using UV–Vis and fluorescence spectroscopy.

2. Materials and methods

2.1. Materials

Recombinant human insulin and thioflavin T were purchased from SAFC Biosciences and Sigma Aldrich, respectively. Anhydrous disodium hydrogen orthophosphate (BDH Chemicals), phenol (Anachemia), glycerol, m-cresol and sodium chloride (Caledon Laboratories) were used as received. Octamethylcyclotetrasiloxane (D₄) (Aldrich), 100 and 1000 cSt trimethylsiloxy-terminated polydimethylsiloxane (PDMS-TMS) (Gelest), 200, 5000, 60,000 cSt PDMS-TMS (Huls America), as well as 3225C Formulation Aid (Dow Corning) were also used as
received. A Dremel tool (Multi PRO, Model 395, Type 5, 442 ½ inch carbon steel brush)[34, 36] was used to produce a high shear mixing environment.

2.2. Solutions of insulin

Aqueous solutions were prepared at two different insulin concentrations: 0.60 mM and 0.05 μM, respectively. For the first, 3.5 mg of dry recombinant human insulin was dissolved in 10 mL of buffer (0.997 mg/mL of anhydrous disodium hydrogen phosphate, 0.58 mg/mL of sodium chloride, 16 mg/mL of glycerol, 1.5 mg/mL of phenol and 1.72 mg/mL of m-cresol, all adjusted to pH 7.7). For the second concentration (0.05 μM), 10 μL of 0.05 mM stock insulin solution (2.904 mg of dry recombinant insulin dissolved in 10 mL of buffer) was added to another 10 mL of buffer.

2.3. General experimental procedure

The effects of different formulation variables (silicone type, molecular weight distributions, concentration, agitation, and mixing times) on insulin stability were analyzed. The latter was indicated by solution turbidity and fluorescence.

2.3.1. Turbidity measurements

Sample volumes (0.3 mL each) of all dispersions (Table 1) were placed in wells of a clear, UV transparent, 96-well Microtest plate from BD Falcon. A Safire Multidetection Monochrometer Microplate Reader from Tecan was used to measure the UV–Vis absorbance scans of each sample from 200 nm to 800 nm and converted to percent transmittance as a measure of turbidity.

2.3.2. Denaturation experiments

The remainders of each mixture (9.7 mL) were centrifuged for 30 min at 4000 rpm using an Eppendorf centrifuge, and the top 4 mL supernatant of each sample was transferred into a separate vial. Solutions of thioflavin T (2.55 mg of dry thioflavin T powder dissolved in 10 mL of buffer, 8 mmol) were made fresh for each experiment. Thioflavin T solution (100 μL) was transferred to each 4 mL aliquot to make 20 μM solutions. Samples (1.5 mL) of these solutions were inserted into clean fluorescence quartz cuvettes and then measured on a Scan Cary Eclipse Fluorescence spectrophotometer, excited at 430 nm and their fluorescence emissions from 435 to 600 nm were recorded. The fluorescence intensity at the wavelength of maximum fluorescent intensity (approximately 480 nm) was taken as a measure of the degree of denaturation experienced by each mixture.
Table 1. Aqueous insulin/silicone dispersions prepared.

| Component viscosity/Blend Name | Silicone oil | Concentration of silicone (wt%) | Concentration of insulin | Shear | Mixing Time (s) |
|--------------------------------|--------------|---------------------------------|--------------------------|-------|-----------------|
| Series 1                       | D4           | 0.001                           | 0.6 mM                   | Low   | 360             |
|                                | D4           | 0.010                           | 0.6 mM                   | Low   | 360             |
|                                | D4           | 0.100                           | 0.6 mM                   | Low   | 360             |
|                                | D4           | 1.000                           | 0.6 mM                   | Low   | 360             |
| Series 1                       | D4           | 0.001                           | 0.6 mM                   | High  | 50              |
|                                | D4           | 0.010                           | 0.6 mM                   | High  | 50              |
|                                | D4           | 0.100                           | 0.6 mM                   | High  | 50              |
|                                | D4           | 1.000                           | 0.6 mM                   | High  | 50              |
| Series 2                       | D4           | 0.001                           | 0.05 μM                  | Low   | 360             |
|                                | D4           | 0.010                           | 0.05 μM                  | Low   | 360             |
|                                | D4           | 0.100                           | 0.05 μM                  | Low   | 360             |
|                                | D4           | 1.000                           | 0.05 μM                  | Low   | 360             |
| Series 2                       | D4           | 0.001                           | 0.05 μM                  | High  | 50              |
|                                | D4           | 0.010                           | 0.05 μM                  | High  | 50              |
|                                | D4           | 0.100                           | 0.05 μM                  | High  | 50              |
|                                | D4           | 1.000                           | 0.05 μM                  | High  | 50              |
|                                | D4           | 0.100                           | 0.6 mM                   | High  | 20              |
|                                | D4           | 0.100                           | 0.6 mM                   | High  | 30              |
|                                | D4           | 0.100                           | 0.6 mM                   | High  | 40              |
|                                | D4           | 0.100                           | 0.6 mM                   | High  | 50              |
|                                | D4           | 0.100                           | 0.05 μM                  | High  | 20              |
|                                | D4           | 0.100                           | 0.05 μM                  | High  | 30              |
|                                | D4           | 0.100                           | 0.05 μM                  | High  | 40              |
|                                | D4           | 0.100                           | 0.05 μM                  | High  | 50              |

(Continued)
| Component viscosity/Blend Name | Silicone oil | Concentration of silicone (wt%) | Concentration of insulin | Shear | Mixing Time (s) |
|-------------------------------|-------------|-------------------------------|--------------------------|-------|-----------------|
| 1000 cSt<sup>a</sup>         | 0.100       | 0.6 mM                        | Low                      | 360   |                 |
| 1000 cSt                      | 0.100       | 0.05 μM                       | High                     | 50    |                 |
| 3225C                         | 0.100       | 0.6 mM                        | Low                      | 360   |                 |
| 3225C                         | 0.100       | 0.05 μM                       | High                     | 50    |                 |
| Bimodal                       | 0.100       | 0.05 μM                       | Low                      | 360   |                 |
| Bimodal                       | 0.100       | 0.6 mM                        | Low                      | 360   |                 |
| Trimodal                      | 0.100       | 0.05 μM                       | High                     | 50    |                 |
| Trimodal                      | 0.100       | 0.6 mM                        | High                     | 50    |                 |
| Broad                         | 0.100       | 0.05 μM                       | Low                      | 360   |                 |
| Broad                         | 0.100       | 0.6 mM                        | Low                      | 360   |                 |
| Narrow                        | 0.100       | 0.05 μM                       | High                     | 50    |                 |
| Narrow                        | 0.100       | 0.6 mM                        | High                     | 50    |                 |

<sup>a</sup> Linear silicone oil capped with SiMe<sub>3</sub> groups: PDMS-TMS 1000 cSt<sup>a</sup>.
2.4. Effect of D₄ on aqueous insulin

D₄ (Me₂SiO)₄, MW 296.62, was selected for use as a model, low molecular weight silicone oil. Each of the insulin solutions above was used to create a corresponding series of dispersions with different concentrations of D₄ 0.104 μL (0.001 wt%), 1.04 μL (0.01 wt%), 10.4 μL (0.1 wt%), and 104 μL (1 wt%) added in each case to 10 mL of insulin in buffer (Table 1). Series 1 was made from 0.6 mM insulin/10 mL of buffer, and Series 2 was made from 0.05 μM insulin/10 mL of buffer.

2.5. Agitation of insulin solutions with different silicones including 1000 cSt blends

The effect of mixing different classes of silicones (low MW, medium MW, surfactant) with insulin was investigated by adding 0.1 wt% of D₄, PDMS-TMS 1000 cSt (narrow) or 3225C (Fig. 1), to 0.6 mM insulin; the same three silicones were separately mixed with 0.05 μM solutions of insulin. Solutions containing silicones and 0.6 mM of insulin were mixed for 4 min at low shear, while solutions of silicone and 0.05 μM of insulin were mixed for 50 s at high shear. Each sample was then examined for turbidity and denaturation.

Four different silicone mixtures were prepared, each of which had a viscosity of 1000 cSt, as determined by using the cone and plate setting in the STRESSTECH rheometer from ATS RheoSystems [34]. The mixtures differed in the types and quantity of silicone oils (PDMS-OTMS) that they contained (Table 2). The effect of these 0.1 wt% silicone mixtures on the turbidity and degree of denaturation for 0.6 mM and 0.05 μM insulin solutions (low and high shear) was measured.

3. Results

It was hypothesized that lower molecular weight silicone oils would have a disproportionate affect on insulin stability [34]. Initially, therefore, the very low molecular weight, highly mobile silicone monomer D₄ ((Me₂SiO)₄, viscosity = 2.5 cSt, Fig. 1) was used to test the effect of silicones on aqueous solutions of insulin. Accelerated tests were performed using higher concentrations of silicone and

![Chemical structures of D₄, 1000 cSt PDMS, and the surfactant DC3225C.](image)
higher degrees of shear than would be expected for most lubricated syringes under normal use.

3.1. Effect of mixing time, agitation and D₄ concentration

Two different concentrations of insulin were mixed with four different concentrations of D₄ under either low or high shear. High shear mixing was achieved using a Dremel tool (5000 rpm) to mix the insulin-D₄ dispersion, while low shear was accomplished using a magnetic stir bar (90 rpm). Transmittance values of the dispersions at 650 nm are shown in Fig. 2, Fig. 3, Fig. 4 (the wavelength was selected to be remote from any absorption due to protein-based chromophores on the proteins). As shown in Fig. 2A, regardless of insulin concentration or shear type, an increase in D₄ concentration led to increased turbidity of the insulin dispersion (lower percent transmittance). The most significant effect was seen between 0.01 and 0.1 wt% D₄, with the latter exhibiting a percent transmittance approximately four times smaller than the former.

Table 2. Total volume in mL and (volume percent %) compositions of different viscosities of PDMS-TMS mixed to make 1000 cSt blends.

| Component viscosity | 100 | 200 | 1000 | 5000 | 6000 |
|---------------------|-----|-----|------|------|------|
| Blend Name          |     |     |      |      |      |
| Bimodal             | 8 (80) | -   | -    | -    | 2 (20) |
| Trimodal            | -   | 5 (36) | 6 (43) | 3 (21) | - |
| Broad               | 1 (8) | 3 (23) | 7 (54) | 5 (15) | - |
| Narrow              | -   | -   | 5 (100) | -    | - |

Fig. 2. A: The effect of different D₄ concentrations on insulin aggregation in the presence of low (stir bar, 90 rpm, 4 min) and high shear mixing (Dremel tool, 5000 rpm, 50 s). B: Effect of mixing time (high shear) on 0.1% D₄-insulin dispersions. In all cases n = 3.
Insulin is quite stable against mechanical damage irrespective of concentration, as judged by its ability to resist shear forces; protein aggregation to form opaque dispersions was not observed (Fig. 2B, controls). However, in the presence of 0.1 wt% D4, the percent transmittance of the more concentrated protein solution at 10 s of high shear mixing was already half that of the corresponding control. The effect of D4 was even more pronounced for 0.05 μM insulin solutions, which showed a 3.8 fold decrease in percent transmittance at the same time point (10 s, Fig. 2B).

Fig. 3. Effect of D₄, medium MW silicone (PDMS-TMS) or a surfactant (3225C) on 0.6 mM (low shear mixing, 90 rpm, 4 min) or 0.05 μM insulin solution (high shear, 5000 rpm, 50 s) based on the ability to form A: opaque dispersions resulting from protein/silicone aggregates. B: denaturation as judged by fluorescence emission at 430 nm. In all cases n = 3.

Fig. 4. A: Percent light transmittance and B: fluorescence intensity changes of insulin solutions that were mixed with 0.1 wt% of PDMS-TMS blends at 5000 rpm for 10 s: higher values reflect a great degree of denaturation. The blends had the same average molecular weights but different molecular weight distributions of silicone oils. In all cases n = 3.
3.2. Effect of different silicone oils

The presence of higher viscosity silicone oils, such as those used in syringe lubricants, was also predicted to cause turbidity of insulin solutions. However, insulin denaturation and aggregation was expected to occur over longer time periods than with low viscosity D₄. In order to separate the effects of dispersion from those of denaturation, low molecular weight silicone D₄ was compared with PDMS-TMS (1000 cSt) and a silicone surfactant 3225C (Fig. 3), each of which were added at 0.1 wt% each to pre-made insulin solutions before the dispersion was agitated.

Mixing the protein solution with the surfactant 3225C led to stable emulsions (Fig. 3). The fluorescence intensity of an insulin solution at 480 nm (excitation at 430 nm) is indicative of changes in protein naturation. Although dispersions readily formed, the surfactant 3225C led to the least denaturation in 0.6 mM insulin dispersions (Fig. 3B). The relatively lower fluorescence intensities indicate minimal thioflavin T binding to insulin β-sheets, meaning that the sheets were predominantly shielded from the exterior, as is normally found with the natured protein.

Mixing insulin solutions with the low molecular weight silicone D₄ led to high degrees of opacity similar to 3225C (Fig. 3). As anticipated, the more viscous silicone PDMS-TMS also facilitated formation of a second phase, but less efficiently than D₄. These changes in opacity were accompanied by an increase in the fluorescence intensity at 480 nm, indicative of protein unfolding: again, the rate of unfolding was faster with D₄ than PDMS-TMS (Fig. 3).

3.3. Effect of different molecular weight

These data suggest that lower molecular weight silicones in particular facilitate both insulin denaturation and aggregation. In light of this, the effect of different mixed silicones on insulin stability was examined in blends that had an identical viscosity of 1000 cSt but with different fractions of lower MW silicones (Table 2). According to Fig. 4, both denaturation and aggregation occurred more efficiently in mixtures containing the largest fractions of low MW materials (bimodal and broad): the narrow blend that contained essentially no low viscosity silicones was associated with the greatest insulin stability.

4. Discussion

Insulin is comprised of two polypeptide chains that are linked together by covalent disulfide bridges. Each chain adopts a secondary structure through hydrogen bonding between the amine and carbonyl groups of alpha carbons in the peptide backbone. The final 3D conformation orients the polar and hydrophobic sides
chains of amino acids towards and away from the aqueous environment, respectively [37].

Insulin monomers can polymerize to varying degrees (hexameric forms, for example, exist in special pancreatic cells after production), however, only the monomeric and dimeric forms are active [37]. Conversely, if and when the structure of insulin is denatured, insulin monomers can irreversibly and undesirably aggregate to form oligomers of misfolded proteins [28]. As a consequence, insulin solutions go from clear to turbid.

The denaturation of insulin can involve the exposure of hydrophobic residues at an interface. Four misfolded monomers attract to make a soluble aggregate termed a ‘seed’, which serves as the nucleation site for additional aggregates to bind and form a fibril [31]. With growing fibrils, the transparency of the solution decreases; hence, the ‘haze’ or ‘veils’ seen in some PFS. Additionally insulin denaturation can lead to the exposure of previously masked residues, which can be tagged with fluorescent probes to study the degree of misfolding. Thioflavin T, for example, interacts with β-sheet structures found in insulin [19]. Normal insulin appears to have low β-sheet content at its surface. During unfolding, however, the β-sheet concentration increases, as internal structures become exposed to the exterior, leading to greater interactions with thioflavin T and, therefore, an enhanced fluorescence emission [38]. Accordingly, the effect of different silicones on aqueous insulin (under agitation for different times) was analyzed using the percent transmittance fluorescence spectroscopy of solutions.

Previously, it has been shown that contact with hydrophobes like poly(vinyl chloride) and polypropylene caused greater denaturation of aqueous insulin than contact with hydrophilic materials (such as polyamide, cellulose butyrate, and titanium) [39]. Increasing the hydrophobicity of such materials, as is the case with lower surface energy silicones, also correlates with greater insulin aggregation [40]. In each case, the natural state of insulin is lost when polar side groups are exchanged for hydrophobic residues at the surface to interact with the new, nonpolar exterior (or D4, as is the case with this report).

Silicones, with their extremely low surface energies, are expected to interact more effectively than organic hydrophobes with the hydrophobic domains of proteins. This may lead, depending on the degree of internal protein crosslinking, to unfolding, as has previously been observed with has [34]. The consequences of such unfolding may be changes in bioefficacy, which we have not examined, and changes in the degree of protein naturation and aggregation.

Contact with silicones has been linked to the aggregation of many different proteins. For example, fibrinogen and fibronectin have been shown to aggregate in the presence of D4; both show increased aggregation with an increasing D4 to
protein ratio in oil-in-water emulsions [17]. Similar trends have been reported for ribonuclease A (RNase A), bovine serum albumin (BSA), and concanavalin monoclonal antibody [30]. In the cases reported, protein aggregation required agitation [11]; more aggregation was a consequence of greater shear [17].

In the case of insulin mixed with the silicone surfactant 3225C, dispersion-related opacity was observed. However, fluorescence intensity measurements indicated minimal denaturation compared to D₄ and PDMS-TMS. In dispersion of 3225C, therefore, proteins were likely entrapped in domains stabilized by surfactants, so the proteins may have been protected from significant denaturation. This could be a consequence of the surfactants’ ability to orient at the interface between hydrophobic oils and the polar side chains of insulin, such that the hydrophilic components of the surfactant interact with the protein while its hydrophobes interact with the oils. These observations allow the separation of turbidity from protein denaturation and aggregation – the two are not necessarily linked. Other studies have also confirmed the mitigative effects of surfactants in commercial formulations of therapeutic proteins [39, 41, 42, 43].

This study demonstrates that the extent to which insulin appears adversely affected on contact with silicones correlates with silicone viscosity. D₄ and PDMS-TMS have comparable, low surface energies, and like all dimethylsilicones (that have not been modified with hydrophilic groups) are essentially insoluble in water. However, they differ significantly in viscosity: 2.5 vs 1000 cSt [29]. The low viscosity fluid D₄ is readily broken into small droplets with high surface area under shear, leading to an unstable dispersion. In the absence of proteins, the dispersions rapidly phase separate into two bulk phases. However, when using a protein solution the insulin can adsorb onto the surfaces of D₄ droplets, which then initiates the unfolding process that, in turn, leads to the permanent aggregation of insulin giving a stable two-phase system. That is, hydrophobic silicone moieties facilitate protein unfolding and a secondary consequence is the formation of an opaque dispersion.

The same process is likely occurring with the higher MW chains of the more viscous PDMS-TMS, since the percent transmittance and fluorescence emission results are similar to the case when was used as the hydrophobic carrier D₄. However, droplet formation is less efficient with higher viscosity materials at the same shear, hence, fewer droplets are formed, which provides an overall lower surface area on which protein unfolding and aggregation can occur; the processes are less efficient [38]. Longer shear times with a given silicone oil (50s vs. 10s, Fig. 3 vs. Fig. 4) provide more droplets and more opportunity for the denaturation/aggregation events of insulin.

Similar patterns were seen for insulin solutions exposed to silicones of identical viscosity but different fractions of lower molecular weight materials. The net rate
of protein unfolding and aggregation tracked with the fraction of lower molecular weight, lower viscosity materials present in a silicone mixture, as seen from Fig. 4: Bimodal 80% 100 cSt > Broad 8% 100 cSt > Trimodal (36% 200 cSt) > Narrow (Table 1).

The likelihood of significant quantities of low molecular weight silicones in syringe lubricants is low. However, materials that are placed under significant stress due to excessive temperatures and motion through shipping, may be sensitive to even small fractions of low molecular silicones over time. The data thus suggests that lubricants for PFS should be devoid of low MW constituents whenever possible, or at least should be tested, to limit the denaturation of therapeutic proteins.

5. Conclusions

Accelerated testing of insulin unfolding and aggregation was undertaken with low and higher viscosity silicones; in the latter case the viscosity typically used in syringe lubricants was examined. While both materials led to denaturation and aggregation, which manifested through the formation of an opaque dispersion, the rates of such processes were faster with the lower viscosity silicones. Similar effects were observed in blends of silicone oils that had identical viscosities, but differing fractions of low molecular weight materials. The unimodal narrow dispersity silicone oil, which contained essentially no low molecular weight silicones, exhibited the lowest impact on the stability of aqueous insulin solutions. Accelerated formation of veils could be affiliated with low molecular weight fractions of silicone oil in lubricated glass syringes, which suggests that low molecular materials should be avoided in silicone syringe lubricants.

Declarations

Author contribution statement

Lamees Nayef: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Madiha F. Khan: Analyzed and interpreted the data; Wrote the paper.

Michael A. Brook: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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