Efficient Ibuprofen Delivery by a Novel Semi-Solid Silicone Formulation: In-vitro and In-vivo Study

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ABSTRACT SUMMARY
An anhydrous semi-solid topical formulation prepared using a novel crosslinked silicone polymer network delivered ibuprofen (IBP) more efficiently than 3 commercial benchmark products. The silicone formulation showed 5.3 times the IBP maximum flux and 18 times cumulative IBP release in 8 hr compared to that of the best-performing benchmark in the in-vitro permeability experiments. An in-vivo study conducted on rats showed 3.3 times the calculated blood AUCs for the silicone formulation over the benchmark. The IBP amount extracted from the excised rat skin was 2.6 times higher for the silicone formulation compared to that for the benchmark.

INTRODUCTION
Polymeric materials provide the matrix for topical semi-solid dosage form. Individual polymers or polymer mixtures have previously been used to modulate the drug release properties due to different drug-polymer interactions. Influence on the drug release properties due to a minute change in the chemical structure of polymers has also been demonstrated. Although silicones are used in pharmaceutical products, their use as a primary polymer in topical semi-solid pharmaceutical formulations is infrequent. Recent developments of novel silicone materials provide an opportunity to investigate their drug delivery efficiencies.

We report, for the first time, on the efficient delivery of IBP from a topically applied anhydrous formulation prepared using a novel crosslinked silicone polymer network swollen in isododecane (ID). The efficiency of the silicone formulation in delivering the IBP was compared with 3 commercial benchmarks in an in-vitro permeability experiment using human cadaver epidermis. The efficiency of the silicone formulation was further examined in an in-vivo study conducted using rats and compared with the best performing benchmark.

EXPERIMENTAL METHODS
The experimental formulations were prepared using the silicone polymer with appropriate amount of propylene glycol (PG), oleic acid (OLAC) and isopropyl alcohol (IPA) containing IBP at 5% w/w. Three commercial benchmarks, a hydroalcoholic gel (B1; 5% IBP), an emulsion based cream (B2; 5% IBP), and a maximum strength hydroalcoholic gel (B3, 10% IBP), were included in the in-vitro permeability experiments.

Investigation of the in-vitro permeability of IBP through human cadaver epidermis was performed at 32°C using a manual Franz diffusion cell console unit with 15.5±0.5 mg formulation dosage in a 0.63 cm² permeation area. Phosphate buffered saline (PBS, pH 7.4) was used as the receptor fluid. Experiments were carried out for 8 hr with sample collections at 0.5, 1, 2, 4, 6 and 8 hr.

An in-vivo study was performed using cannulated Fischer 344 male rats (Rattus norvegicus). About 450 mg of placebo silicone formulation (n=1), silicone formulation (n=5) or benchmark (B1; n=4) were applied on 10 cm² area of the back of the animals. Blood collection was performed at 0.25, 0.5, 1, 2, 4 and 8 hr post-application. At the end of the study animals were euthanized, formulation dose site was excised and the IBP entrapped in the skin was determined.

The samples from in-vitro and in-vivo studies were analyzed using appropriate UPLC/HPLC methods to determine the IBP concentration.

RESULTS AND DISCUSSION
Figure 1 shows the in-vitro IBP release profiles of the silicone formulation and benchmarks. The silicone formulation showed the highest flux of 28.9 μg/cm²/hr at 4 hr and a cumulative IBP release of 108.8 μg in 8 hr. The best performing benchmark (B1) showed its highest flux of 5.5 μg/cm²/hr at 1 hr and a cumulative 5.9 μg of IBP in 8 hr. The average IBP released from the silicone formulation was 12.9% and 0.7% for B1.

![Figure 1. In-vitro IBP permeability profiles of silicone formulation and 3 commercial benchmark products.](image-url)
The efficient delivery of the silicone formulation was further investigated by making similar silicone formulations with low IBP amounts. Figure 2 shows the permeability profiles of silicone formulations prepared containing IBP at 1, 2, 4 and 5%. Formulations with 1 and 2% IBP delivered lower amount of IBP at 30 min compared to B1, however the cumulative IBP amount delivered was higher than B1 in 8 hr for all the silicone formulations.

![Graph showing permeability profiles](image)

**Figure 2.** In-vitro IBP permeability profiles of silicone formulations with low IBP amount.

The IBP delivery efficiency of silicone formulation observed in in-vitro investigation was further corroborated through an in-vivo study. Figure 3 shows the average IBP blood concentration for animals dosed with the silicone formulation (n=5) and B1 (n=4). The maximum IBP blood concentration observed at 1 hr ranged from 14.2 to 28.9 µg/g for silicone formulation. The maximum IBP blood concentration ranged from 2.7 to 5.6 µg/g for B1. Upon comparison, the silicone formulation delivered an average of 2.7, 5.3, 8.7, 4.2, 1.2 and 1.3 times IBP compared to B1 at 0.25, 0.5, 1, 2, 4 and 8 hr respectively. The calculated blood AUCs were 59.2 µg-hr/g and 17.6 µg-hr/g for silicone formulation and B1 respectively (p=0.0027).

![Graph showing IBP in blood concentration](image)

**Figure 3.** Comparison of average IBP blood concentrations measured in-vivo for silicone formulation and B1.

The skin at the formulation dose site was excised after euthanization and the IBP entrapped in the skin was determined. The skin from the animals dosed with silicone formulation contained an average of 264±59 µg/g and the skin from the animals dosed with B1 contained an average of 102±5 µg/g. This indicated the improved local delivery of IBP by silicone formulation compared to B1.

**CONCLUSION**

The silicone based formulation delivered the IBP more efficiently in terms of flux, cumulative amount and percent drug release compared to 3 commercial products according to the results obtained from in-vitro permeability experiments. Silicone formulations containing less IBP also showed greater cumulative drug release than benchmark. This was further supported by the results obtained in the in-vivo study conducted on rats using silicone formulation and B1. The silicone formulation delivered an average of 2.7, 5.3, 8.7, 4.2, 1.2 and 1.3 times IBP systemically compared to B1 at 0.25, 0.5, 1, 2, 4 and 8 hr respectively. The IBP amount in the excised skin from the dose sites was 2.6 times higher for silicone formulation compared to that for benchmark.

The results obtained from in-vitro and in-vivo studies clearly support the efficient delivery of IBP from a silicone formulation over multiple commercial benchmarks.

**REFERENCES**


**ACKNOWLEDGMENTS**

The authors would like to thank National Disease Research Interchange (NDRI, Philadelphia, PA) with support from NIH grant 5 U42RR006042 for providing custom harvest human cadaver skin tissues.