EFFECT OF PETROLATUM SOURCES AND DIFFERENT MANUFACTURING PROCESSES ON PHYSICOCHEMICAL AND DRUG RELEASE RATE OF TOPICAL OINTMENTS

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BACKGROUND

It is well known that generic products that have qualitative (Q1), quantitative (Q2) and formulation microstructure (Q3) similarity are likely to act in a similar manner to the reference listed drug (RLD) that is listed in the FDA Orange Book. Q3 pertains to comparable microstructure and includes physicochemical properties and drug release rate. Topical dermatological formulations often require many excipients, and correct excipient selection is important for generic topical drug product development, since the resulting microstructural and physicochemical characteristics of the product can greatly influence topical bioavailability.

This is the case for white petrolatum which is often a major ingredient in petrolatum-based topical ointments. Different sources of white petrolatum that comply with the same pharmacopeia grade may result in prototypes with different physicochemical properties, thus potentially affecting the drug release profile[1]. So, whilst meeting Q1 and Q2, the formulation may not be Q3.

AIM

To investigate the influence of three different sources of white petrolatum on the viscosity, microscopic appearance and the *in vitro* drug release rate of the ointment prototypes. Additionally, to assess the effect of different manufacturing processes using one petrolatum source on the viscosity and drug release rate.

All obtained data will be compared to the RLD data.

METHODS

Formulation preparation:
Prototypes #1-3 were prepared with three different sources of white petrolatum (at ~90%w/w), using the same manufacturing process.

Prototypes #4-6 were prepared with the same petrolatum as Prototype #1 (the composition remained the same), however using different manufacturing processes, refer to Table 1.

Microscopy:
Formulation appearance was examined using an Olympus SZX12 Microscope (Olympus Australia Pty Ltd) at x90 magnification. Normal and polarized view were both recorded (n=3).

Viscosity Measurement:
Viscosity of each formulation at 25ºC was measured using a Brookfield CAP 2000+L Viscometer (AMETEK Brookfield, US) (n=2).

***In Vitro* Release Test (IVRT):**
Vertical Franz-type diffusion cells with a synthetic membrane was used to determine the drug release rate where the cumulative amount released (µg/cm^2) versus square root of time (h$^{1/2}$) was plotted (n=2-3).

RESULTS AND DISCUSSION

The representative microscopic images of ointment prototypes prepared with three different sources of white petrolatum are shown in Figure 1. It is evident that the microscopic appearance of Prototypes #1, #2 and #3 were comparable to each other and to the RLD. However, Prototypes #1 and #2 both exhibited higher viscosity compared to Prototype #3 and were also observed to be comparable to the RLD (Table 1).

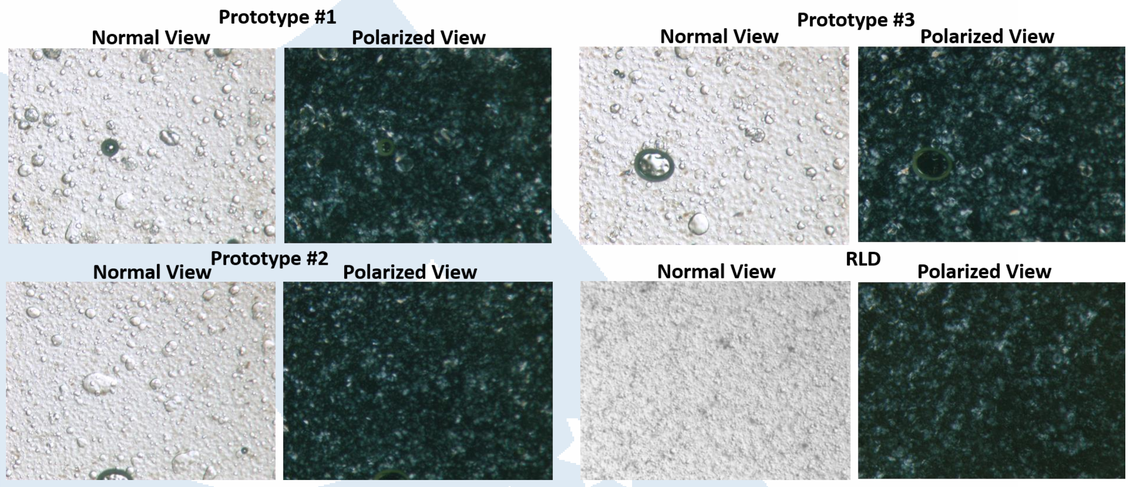


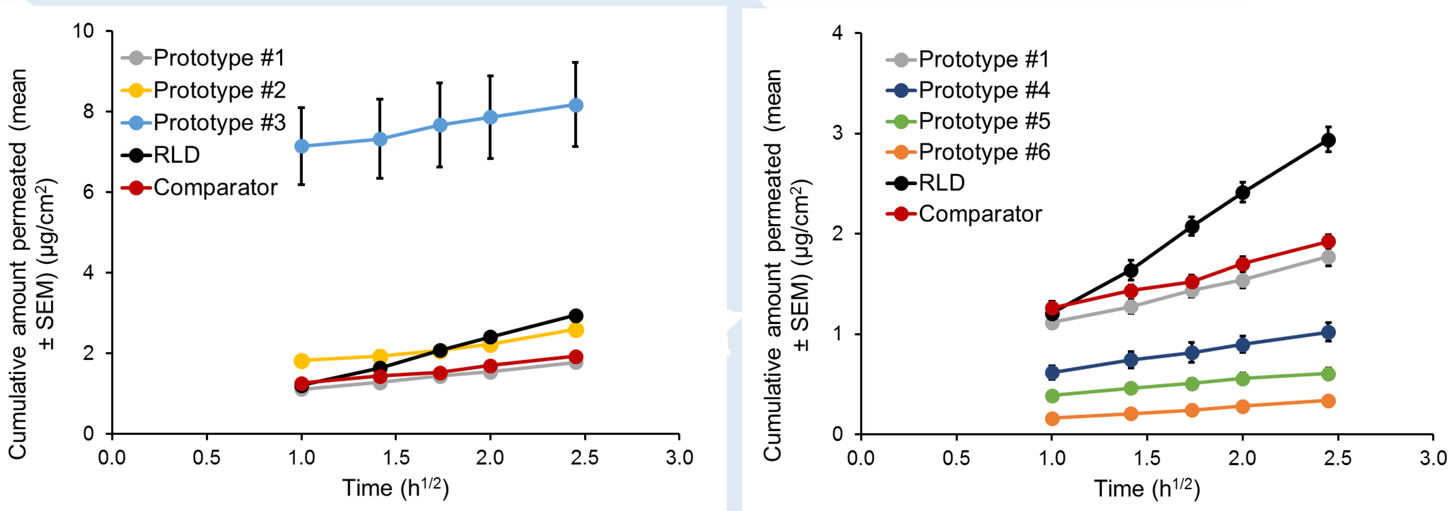
Figure 1. Microscopy at x90 magnification of RLD and prototypes prepared with different white petrolatum

Using different manufacturing methods in terms of homogenisation, stir cooling, and temperature, it was observed that the resultant viscosities were slightly different when comparing Prototypes #4, #5 and #6 to Prototype #1.

Table 1. Viscosity of prototypes prepared with different white petrolatum and different manufacturing processes

Sample	White Petrolatum	Manufacturing process	Viscosity (mean ± SD), (cP)
Prototype #1	Source A	Homogenised and then cooled to 25ºC with stirring	21605 ± 35
Prototype #2	Source B	Homogenised and then cooled to 25ºC with stirring	18380 ± 382
Prototype #3	Source C	Homogenised and then cooled to 25ºC with stirring	13620 ± 382
Prototype #4	Source A	Homogenised and then cooled to 40ºC with stirring	29615 ± 2666
Prototype #5	Source A	Homogenised and then cooled to 25ºC without stirring	29590 ± 2913
Prototype #6	Source A	No homogenization and then cooled to 25ºC without stirring	28475 ± 4278
RLD	Unknown	Unknown	18930 ± 665

IVRT results (Figure 2a) showed that Prototypes #1 and #2 with a higher viscosity, displayed a lower drug release compared to Prototype #3 which suggested that the viscosity of the prototype ointment could be used as an indicator of its IVRT drug release rate. Additionally, manufacturing processes such as homogenization and cooling temperature could also affect drug release rate (Prototypes #1, #4, #5, and #6 in Figure 2b).



(2a) (2b)

Figure 2. Cumulative drug release (mean ± SEM) from different prototypes compared to marketed products

CONCLUSION

Different sources of petrolatum could not be assumed to produce similar release of the drug from the ointment matrix. Additionally, in line with ICHQ8(R2), critical process parameters should be established to ensure critical quality attributes of the formulations. Thus, during development of topical ointments, the selection of excipients such as white petrolatum and manufacturing processes may have an impact on physicochemical properties and IVRT drug release rate of the product.

REFERENCES

1. In Vitro Characterization of Topical Semisolid Dosage Forms, Raney S, presented at 3rd PQRI/FDA Conference on Advancing Product Quality, March 22nd, 2017

ACKNOWLEDGEMENTS

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