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Short communication

Selection of membrane filter for in vitro release test method for PEG-based ointment

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Introduction

As semi-solid topical formulations become more prevalent, the *in-vitro* release testing (IVRT) is playing an important role in determination of the release performance and diffusion of these drug products (PermeGears-Guide-to-Choosing-a-Membrane). Per It is an effective research and development technique, and it can be used to develop and optimize the semi-solid drug formulations (Olejnik et al., 2012).

The IVRT measures the rate of release of the active pharmaceutical ingredient (API) from the drug product across an inert membrane into an appropriate receiving medium. Therefore, it allows an appropriate selection of a clinical candidate with Quality-by-Design principles, and it can serve as a cost-effective means to monitor the drug product consistency. An appropriate IVRT testing method needs to mimic skin permeation kinetics, including donor, membrane and receptor medium that is analyzed for the drug concentration.

Selection of appropriate membrane filter is one of the critical steps in IVRT method development. Commercially available membrane filters differ in diameter, pore size, thickness, chemical composition and type of porosity. Ideally, membrane filters used for IVRT should provide minimal resistance to the API diffusing out of the formulation, while completely retaining all other components of the formulation. The membrane pore size should be large enough, thus the API could easily diffuse through, but the other formulation components should be retained. (Kafner et al., 2017). Also, membrane inertness is an important factor since the chemical composition of membranes may affect the degree to which other molecules may be bound or absorbed by them (EMA – draft guideline on quality and equivalence of topical products).

The aim of this study is selection of an appropriate membrane filter for IVRT method for polyethylene glycol (PEG) - based ointment.

Materials and methods

The experiments were performed on vertical diffusion cell (Franz cell system) manufactured by Hanson Research Corporation. Five different types of membrane filters were used: three types of hydrophilic membranes such as regenerated cellulose (RC), cellulose acetate (CA) and polyethersulfone (PES), and two types of hydrophobic membranes – polytetrafluoroethylene (PTFE) and StratM membrane (according to the data from the manufacturer - mimics human skin). All membranes used were with 0.2 μm pore size.

The medium used for performing the tests consists of a mixture of 10% phosphate buffer solution and ethanol in a ratio of 60 / 40 (V/V). Ethanol is included in the medium in order to achieve sink conditions, since the API has low solubility in water. The tests were performed at temperature of 32°C $\pm$ 0.5°C, which imitates the temperature of the human body skin.

In each of the 6 cells, about 730 mg of the ointment was applied, which is equal to 14.3 mg of API. The test was performed for 5 hours, and samples were taken at 7 different time points: after 10 minutes, 30 minutes, 60 minutes, 120 minutes, 180 minutes, 240 minutes and 300 minutes.

Quantification was performed on HPLC Agilent 1290 Infinity Automated system, with an in house developed HPLC method. Thermo Hypersil Gold 150 x 4.6 mm

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HPLC Column was used for the HPLC analysis. The mobile phase consists of a mixture of acetic buffer – consisting of 1.925 g/L ammonium acetate adjusted to pH 5.0 with glacial acetic acid, and Acetonitrile in a ratio of 65 / 35 (V/V). The flow rate is 1.5 ml/min, and the run time is 9 minutes, with an injection volume of 2 µL. The detection wavelength is 228 nm.

Results and discussion

Drug release from semi-solid dosage forms follows the Higuchi kinetics. According to this, the amount of drug released is proportional to the square root of the time. Therefore, a plot of the cumulative amount of released API versus the square root of the time is created for each of the applied samples. The slope of the plot shows the drug release rate for each of the samples.

For the hydrophilic membranes, the average cumulative amount of API per cm^2 at the end of the test is 3270 $\mu g/cm^2$ for the RC membrane, 3852 $\mu g/cm^2$ for the CA membrane, and 4353 $\mu g/cm^2$ for the PES membrane, which equals to 39.6%, 46.6% and 52.7% of the applied API, respectively. The variability between the samples in the final sampling point, presented as relative standard deviation, is 17% for RC membrane, 8% for CA membrane and 16% for PES membrane. The average drug release rate is 1720.5 for the RC membrane, 1996.3 for the CA membrane and 2341.7 for the PES membrane.

For the hydrophobic membranes, the cumulative amount of API per cm^2 at the end of the test is 2499 $\mu g/cm^2$ for the PTFE membrane, and 466 $\mu g/cm^2$ for the StratM membrane, which equals to 30.2%, and 5.6% of the applied API respectively. The average drug release rate is 1361.3 for the PTFE membrane and 221.4 for the StratM membrane. The RSD between the samples in the final sampling point is 47% for PTFE membrane and 82% for PES membrane. This indicates that the variability between the samples is much higher when the hydrophobic membranes are used, compared to the hydrophilic membranes. Also, the cumulative amount of released API and the drug release rate are lower. This is especially evident for the StratM membrane, which inhibits the diffusion of the API from the matrix to the receptor medium. The correlation coefficient is above 0.9 for all of the applied samples for all of the tested membranes, except for the StratM membrane, which has correlation coefficient lower than 0.9. This indicates that the release kinetics for the API is linear for the entire duration of the test.

Additionally, membrane inertness was tested for the hydrophilic membranes, in order to check if the API adheres to any of the membranes. This was performed by preparing three standard solutions in the same concentration as the working standard used in the method. The standards were analyzed after preparation, and after that each of the tested membranes was placed in one of the standards. The flasks were heated at 32 °C for 5 hours, and the standards were analyzed again after the period of 5 hours. Recovery was calculated for each of the standards. The recovery was in the range 98% - 102%, which indicates that the membranes are inert, and there is no interaction between the membrane and the API.

Conclusion

From this study, it can be concluded that hydrophobic membranes are not suitable for IVRT testing of the PEG-based ointment formulation. The high variability between the samples, and the low cumulative amount of API released for the duration of the test, limit the use of those membranes for further use.

Hydrophilic membrane filters, as regenerated cellulose, cellulose acetate and polyethersulfone show lower variability, and linear release kinetic for the duration of the test. Furthermore, membrane inertness has been demonstrated for the three types of membrane filters. Therefore, it can be concluded that hydrophilic membranes are suitable to be used for evaluation of the release of the API from the PEG based ointment formulation.

References

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