Membrane-Drug Binding and its Impact on *In Vitro* Release of Dexamethasone

Catheleeya Mekjaruskul[1], André O'Reilly Beringhs[1], Wei-Chung Luo[1], Qingguo Xu[2], Matthew Halquist[2], Bin Qin[3], Yan Wang[3], Xiuling Lu[1]*

[1]Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, USA, [2]Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University, USA, [3]Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, U.S. Food and Drug Administration, USA. *Corresponding author: xiuling.lu@uconn.edu

aaps 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

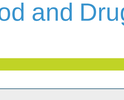
BACKGROUND

In vitro release studies have been widely employed to assess product performance of topical drug products for product development, quality control, and support post-approval changes to the drug product. If membranes bind with drug molecules, mass transport through the membrane will be obstructed or retarded. It is crucial to choose membranes that do not exhibit membrane-drug binding in order to develop a reliable and robust drug release testing method and ensure accurate quantitative analysis.

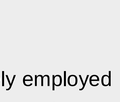
OBJECTIVE

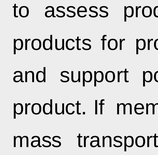
The aim of this study was to investigate the drug binding to membranes and the effect of various membranes on the release performance of a hydrophobic model drug, dexamethasone (DEX).

METHOD(S)

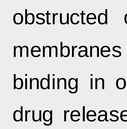


Membrane binding study
1) Syringe filter testing
2) 24-h incubation method

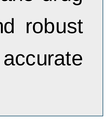




***In vitro* release tests** using USP Dissolution Apparatus IV (Flow-through cell) with semisolid adapter



Morphology analysis under scanning electron microscope (SEM): Nova Nano SEM 450



RESULTS

Table 1 Membrane materials and pore sizes as reported by manufacturers and thickness measurements

Code	Materials	Pore sizes (µm)	Suppliers	Thickness (mm, mean±SD, n=3)
M-I	polyethersulfone	0.45	Sterlitech®	0.13±0.01
M-II	polyethersulfone	0.45	Merck Millipore®	0.14±0.01
M-III	polyethersulfone	1.20	Sterlitech®	0.12±0.01
M-IV	cellulose acetate	0.45	Whatman®	0.13±0.01
M-V	cellulose acetate	0.45	Sterlitech®	0.08±0.01*
M-VI	cellulose acetate	0.45	Sartorius®	0.12±0.00
M-VII	nylon	1.20	Merck Millipore®	0.19±0.01*

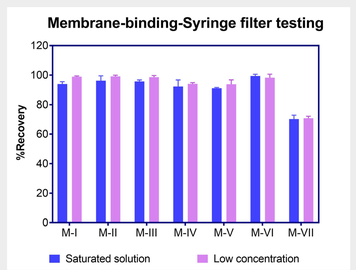


Figure 1 DEX recovery in filtrate following passage through membranes comprised of different materials and pore size using syringe filter testing (mean±SD, n=3)

M-I to M-VI provided DEX percent recovery values of more than 90%, while M-VII showed the lowest percent recovery among all the membranes tested ($P<0.05$), reaching less than 80% recovery for both solutions (Figure 1).

The three polyethersulfone membranes (M-I, M-II, and M-III) provided percent recovery values of more than 90%, whereas cellulose acetate (M-IV, M-V, M-VI) and nylon (M-VII) membranes provided percent recovery values of less than 90% (Figure 2)

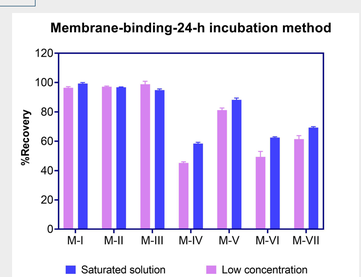


Figure 2 DEX recovery following a 24h incubation of membranes in saturated DEX solution and low concentration DEX solution. (mean±SD, n=3)

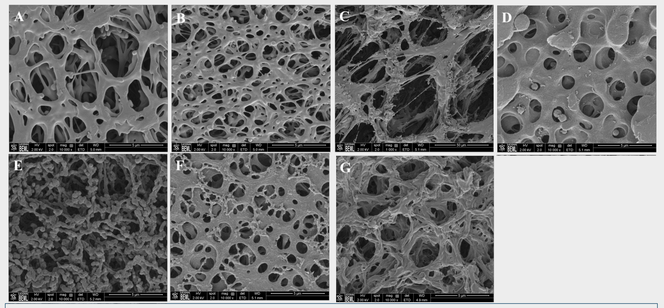


Figure 3 Morphological analysis of the various membranes under SEM (A: M-I, B: M-II, C: M-III, D: M-IV, E: M-V, F: M-VI, and G: M-VII)

The photomicrographs revealed the opening orifices and tortuosity of membrane structures (Figure 3). The largest pore diameter was found in M-III. Whereas, the membrane displaying the least porosity was M-IV.

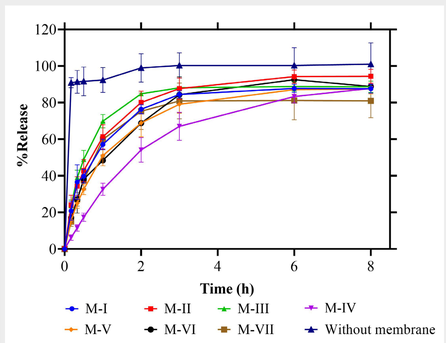


Figure 4 *In vitro* release profiles of DEX solutions in semisolid adapter through various membranes compared with the release profile without a membrane (mean±SD, n=3)

DEX solution diffusion through membranes was significantly slowed down in all the tested membranes when compared with a control experiment where no membrane was used (Figure 4). The release profile of DEX solutions through M-IV was significantly different when compared with those profiles obtained using 0.45 µm membranes from other sources.

CONCLUSIONS

- ❑ Material and source of membranes affected drug dissolution profiles and showed membrane-drug binding effects.
- ❑ Membranes made of the same material with the same labeled pore size but from different manufacturers yielded different release profiles.
- ❑ Proper selection of membranes with low drug binding ability and low diffusion resistance is essential to ensure accurate and reproducible drug release results without any interference from membranes.
- ❑ Cautions should be taken when switching membranes from different sources.
- ❑ The results of this study may be extended to other compounds and lay the ground for validation procedures needed to ensure the appropriate selection of membrane for future *in vitro* release studies.

FUNDING

This study was supported by the U.S. Food and Drug Administration through Contract No. HHSF223201810114C. The views expressed in this paper do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

UCONN | SCHOOL OF PHARMACY

FDA U.S. FOOD & DRUG ADMINISTRATION