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Investigating the Driving Force of Membrane Transport of Carvedilol from Supersaturated Solutions Achieved by Electrospun Formulations

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PURPOSE

When a **poorly water-soluble active pharmaceutical ingredient** (API) is formulated to enhance its dissolution, additives, such as surfactants, **polymers** and cyclodextrins have an effect not only on **dissolution** profile, but also on **flux** through the membrane. In order to fully understand these effects on flux, the driving force of **membrane transport** cannot be simplified to the total concentration gradient.

OBJECTIVE(S)

The aim of this study was to investigate **the impact of formulation excipients**, solubilizing additives on dissolution, **supersaturation and membrane transport** of an API.

METHOD(S)

Carvedilol (CAR), an anti-hypertensive drug was chosen as a poorly water-soluble model drug and formulated in order to enhance its bioavailability using solvent-based electrospinning. A polyvinylpyrrolidone (**PVP**) derivative (**VA64**) and **Soluplus®** were used to create two different amorphous solid dispersions (ASD) of the API.

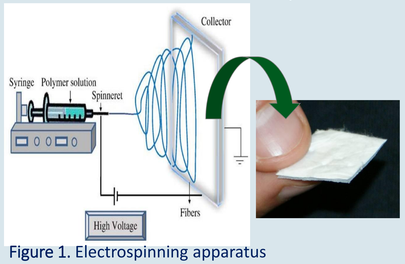

Figure 1. Electrospinning apparatus

The polymer and the API (88:12) were added into ethanol and stirred by a magnetic stirrer at 600 rpm until the dissolution completed. The electrical potential applied on the spinneret electrode was 40 kV . A grounded aluminum plate covered with aluminum foil was used as collector (20 cm from the spinneret). Polymer solutions were dosed with 8-10 mL/h.

The load dependent effect of various additives that can influence the characteristics of dissolution and absorption through artificial membrane (cellulose membrane with 1 kDa MWCO) were observed by carrying out a simultaneous dissolution-absorption study with a side-by-side diffusion cell, µFLUX™. The solubilizing effect of the polymers were studied by carrying out thermodynamic solubility assays in pH 6.5 phosphate buffer (same as the donor media in the dissolution-permeation assays).

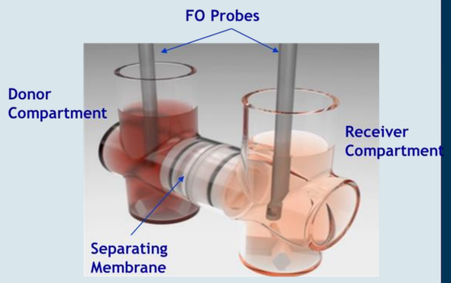

Figure 2. A fragment of the µFLUX™ apparatus showing a pair of the donor and receiver chambers

RESULT(S)

I. Results of thermodynamic solubility measurement of pure API in the presence of different amount of additives

Which polymer is the better solubilizing agent?

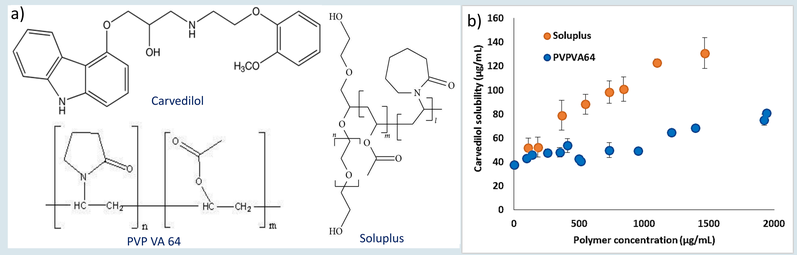

Figure 3. a) Structure of the API and polymer additives; b)Carvedilol solubility as a function of the amount of polyme additive

II. Results of flux experiments of electrospun formulations and the pure API

Is the membrane transport through size exclusion membranes concentration driven?

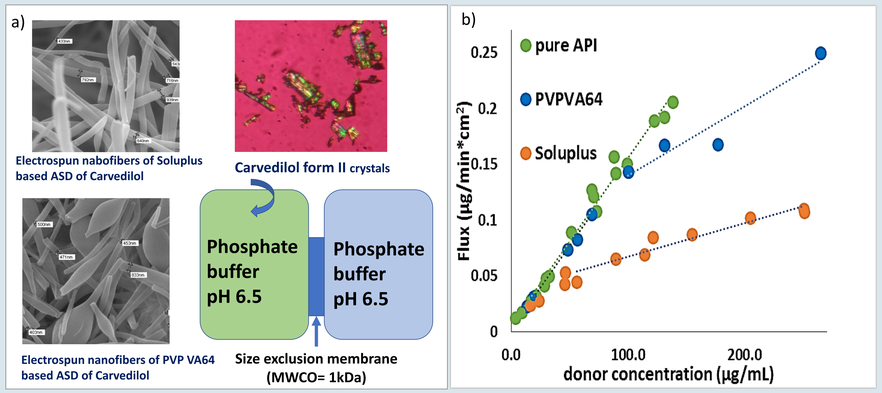

Figure 4. a) Schematic of flux setup showing experimental conditions and microscopic images of the electrospun formulations and the pure API; b) flux of pure CAR and CAR containing ASDs at 25°C as a function of concentration in the donor chamber

While the flux was found to be directly proportional to the donor concentration in the concentration range of 0-100 µg/mL in case of the pure API and the PVP VA 64 containing formulation as well, reaching higher concentrations in the donor chamber resulted in lower fluxes than expected in case of PVPVA 64 containing formulations (Figure 4.b). The similar phenomenon happened for Soluplus containing formulation even in the lower concentration region.

III. What is the real driving force of membrane transport?

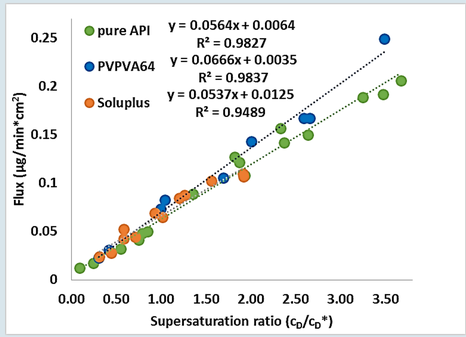

Figure 5. Flux as a function of supersaturation ratio defined as the ratio of the donor concentration and the thermodynamic solubility of the API in the same media

CONCLUSION(S)

Although the solubility assays showed that **Soluplus® was a more powerful solubilizing agent** for the poorly water-soluble Carvedilol than the PVP derivatives, the **amount of drug absorbed through the artificial membrane was found to be significantly smaller** in case of Soluplus® containing formulations. These results clearly indicated that the driving force of membrane transport could not be simplified to the concentration gradient.

Supersaturation ratio (defined as the ratio of dissolved amount of the drug to its thermodynamic solubility in the same media) was found to be the **driving force** of membrane transport.

REFERENCES

RAINA ET AL. IMPACT OF SOLUBILIZING ADDITIVES ON SUPERSATURATION AND MEMBRANE TRANSPORT OF DRUGS. PHARM. RES. 2015, 32, 3350-3364.

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