Controlled release acceleration of lipophilic drug from PEVA-based implants using hydrophilic additives

Zilin Mo, Andriy Dashevskiy, Anne Seidlitz and Roland Bodmeier
College of Pharmacy, Freie Universität Berlin, 12169 Berlin, Germany

Key findings

- Slow risperidone release from PEVA
- Ripseridone release accelerated with lactose as pore-former
- Release acceleration independent of drug loading
- Controlled and predictable release acceleration

Background

Polyethylene vinyl acetate (PEVA) is used as long-acting drug delivery carrier. However, slow release rates limit its applicability for some drugs [1]. Addition of lactose (LAC) as a pore-former can increase drug release [2]. The aim of the study was to evaluate lactose addition for drug release acceleration from PEVA matrices.

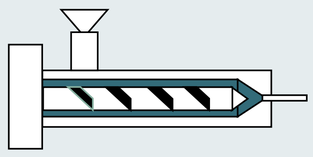
Materials & Methods

Materials

Drug: risperidone (RIS)
Hydrophilic additive: InhaLac 500 (LAC)
Polymer: Elvax 40w (PEVA 40)
(loading based on the total weight)

Preparation

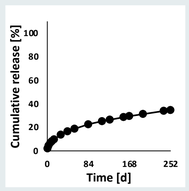
Hot-melt extrusion
HAAKE MiniLab CTW5
100°C, 20 rpm
Die diameter = 1 mm
Cut length = 10 mm



Characterization

Incubation
PBS pH 7.4
37°C, 80 rpm, n = 3

Microscopic observation



In-vitro Release

Medium uptake

Results & Discussion

Risperidone release from PEVA matrix was slow, reaching 40% after 28 days. The release increased gradually with increasing lactose content up to 25% (Fig. 1A). Since the release profiles of both risperidone and lactose followed Higuchi kinetics ($R^2 > 0.97$), the quantitative relationship between the release rate (slope of Higuchi plots) and lactose loading was analyzed (Fig. 1C). This relationship exhibited two distinct changes in slope, indicating lactose percolation behavior. Below the first threshold (e.g., 5% lactose), lactose osmotically attracted release medium without remarkable release (Fig. 1B), resulting in visible matrix swelling (23% volume increase). In this case, isolated hydrated pores were formed, inducing polymer structural changes, and thus, facilitating drug diffusion. In the second phase (10 – 25% lactose), lactose release increased gradually with loading, leading to formation of interconnected pore network, while matrix swelling became less pronounced. Therefore, the effect of lactose loading on porosity and release rate acceleration was reduced. Above the second threshold (e.g., 50% lactose), lactose leached rapidly out (Fig. 1B) and the matrix shrunk (24% volume decrease), resulting in plateau in drug release acceleration.

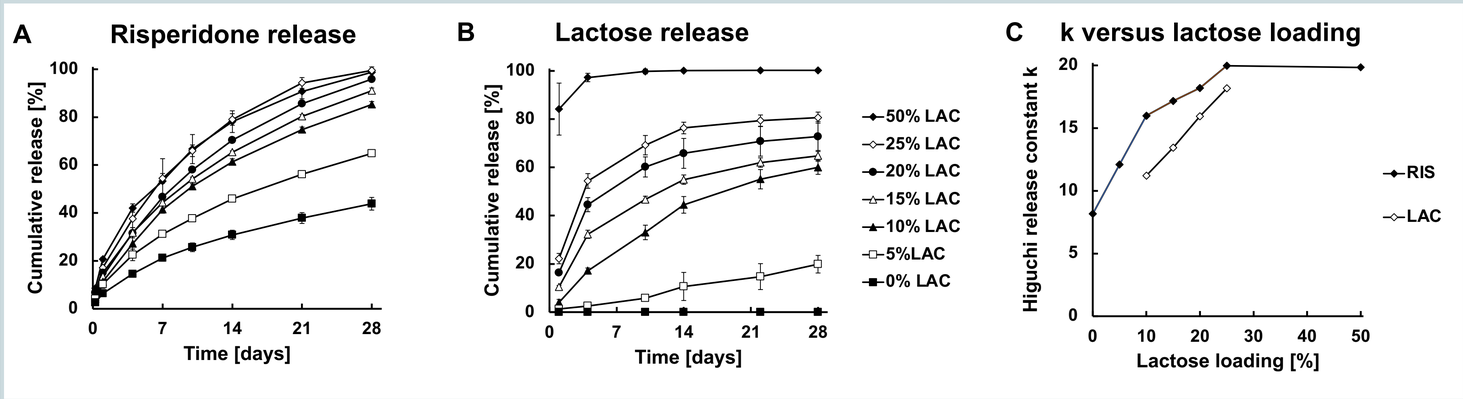


Fig. 1: Risperidone and lactose release from 20% drug loaded implants

The acceleration extent in both drug release and medium uptake was independent of risperidone loading at the same lactose loading (Fig. 2A and 2B). Risperidone dissolved favorably in the polymer and diffused through the polymer either to the surface area of the matrix or to the next available interfacial area of pores, resulting in an increased release (Fig. 2D). The matrix porosity is affected mainly by lactose release rather than by risperidone. Thus, the increase in risperidone loading did not contribute to the porosity as demonstrated by microscopic observations (Fig. 2C).

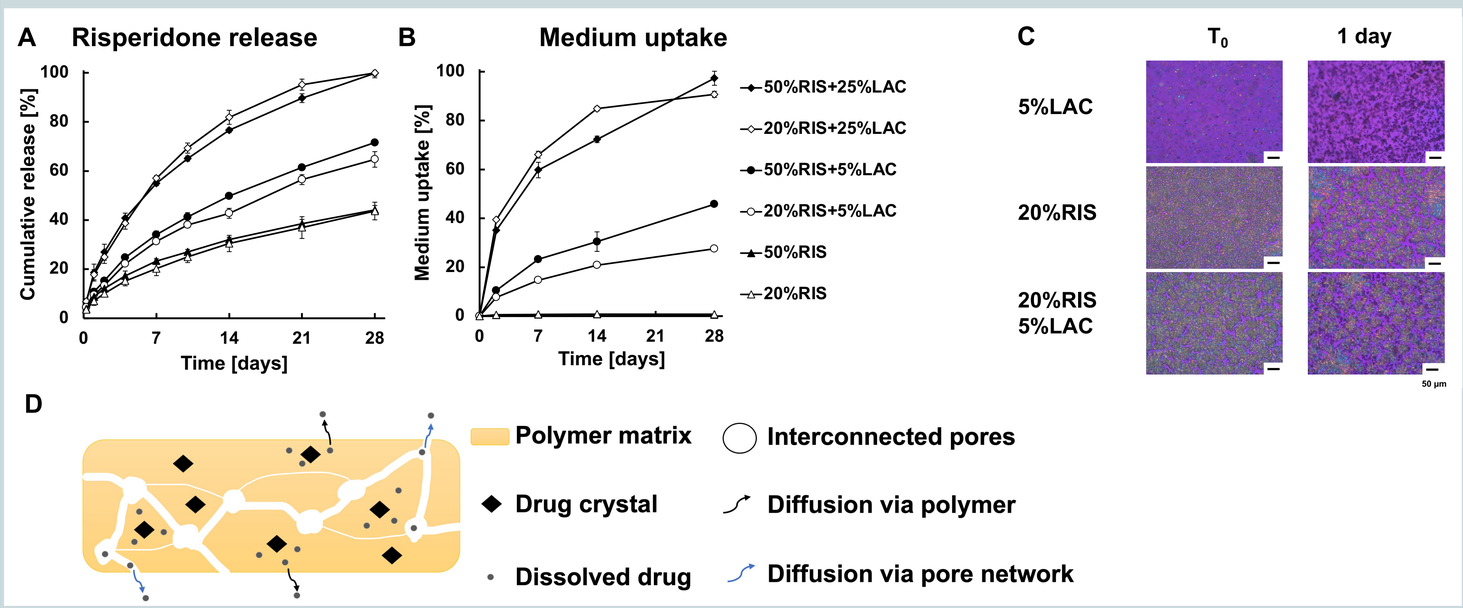


Fig. 2: Effect of risperidone loading on release

Conclusion

Gradual acceleration of risperidone release from PEVA matrices was achieved by addition of lactose in increasing amounts, which induced an increased porosity resulting in additional diffusion pathways and increase in interfacial area for partitioning. The acceleration was independent of drug loading. These findings demonstrate the potential of lactose to accelerate drug release from PEVA matrix in a controlled and predictable manner.

References

[1] Genina N et al., Eur J Pharm Sci., 2016

[2] Janssen PHM et al., Eur J Pharm Biopharm., 2022

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Contact: zilin.mo@fu-berlin.de