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Experimental Investigation of the Release Mechanism of Hydrophilic Solutes from Hydrophobic Matrices

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1. Introduction

The controlled release of drugs from hydrophobic polymer monoliths is facilitated markedly by the presence of water-soluble excipients [1]. However, the release profiles of the water-soluble excipients and the organic molecules are governed by different release mechanisms. In the former case, the osmotic action of the water-soluble excipients causes excessive sorption of water, which in turn may give rise to non-Fickian release kinetics. On the other hand, the release of a drug (regardless of whether its initial concentration in the matrix is above or below its solubility in the polymer), frequently follows $t^{1/2}$ (t=time) kinetics. Various models have been proposed to account for the observed kinetic behavior [2-4].

In this work we report a comparative study of the kinetics of release of a water-soluble inorganic salt (NaCl) and a model drug (proxyphylline). The study was supplemented by parallel measurements of (i) the concurrent variation of the water content of the matrices (ii) the permeation properties of the depleted matrices and (iii) the mechanical properties of loaded and depleted matrices.

2. Results

Pre-polymer mixtures (10:1) of silicone rubber (SR) type GE-615 (GE- Silicones), were cast by means of a doctor knife and cured at 100^{o}C to obtain the final crosslinked matrices. The salt/drug loaded matrices were obtained by adding NaCl (osmotically active excipient of particle size 7-8 μm) and proxyphylline (model drug of particle size ca 1μm), to the fluid SR mixture prior to casting. Salt or drug release from these loaded films was measured along with the concurrent variation of the water content of the films. Comparative values of the tensile modulus of elasticity of dried neat, loaded and salt or drug-depleted, films were obtained by means of a Tensilon instrument.

Plots of amount salt released versus $t^{1/2}$ are shown in Fig. 1a. The release curve is S-shaped, indicating acceleration of salt release due to osmotically-induced sorption of excess water. On the other hand, the release of the drug (Fig. 1c) follows $t^{1/2}$ (Higuchi) kinetics. In both cases the water uptake reaches a maximum value, followed by a decline to a final value in the salt depleted matrices, which is more pronounced in the case of NaCl.

In the case of NaCl, the large excess of imbibed water presumably leads to the formation of cracks. Crack formation is also in line with the measured diffusion coefficients of NaCl in the depleted matrices, which are of the order of 10^{-7} cm^2/s. On the other hand, in the case of the drug, release appears to occur by diffusion through more uniformly swollen polymer without formation of cracks and is relatively little affected by

the presence of excess imbibed water. This is also in line with the drug diffusion coefficients, in the drug-depleted matrices, which were found to be of the order of 10^{-9} cm^2/s.

Furthermore, dried salt- and drug-depleted films exhibited similar significant decrease in the Young's modulus relative to neat films attributable to healing of the cracks in the case of NaCl and the presence of cavities left behind by the released solute particles in both cases.

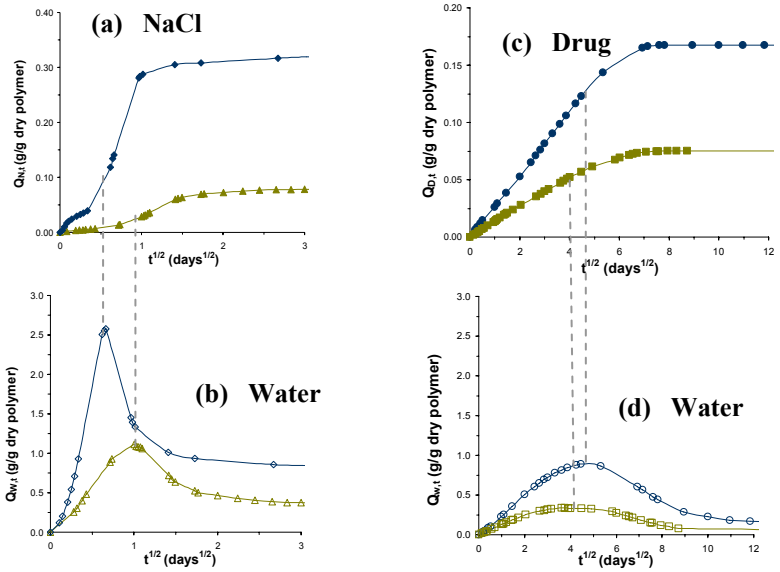

Fig. 1: (a) Salt release kinetic curves on a $t^{1/2}$ scale for volume fraction 0.04 (▲) and 0.13(♦)
(b) Corresponding variation of osmotically induced excess water uptake.
(c) Drug release kinetic curves on a $t^{1/2}$ scale for volume fraction 0.05 (■) and 0.11(●)
(d) Corresponding variation of osmotically induced water uptake.

3. Conclusion

The non-Fickian release kinetics of the strongly osmotically active NaCl is attributable to the presence of a large excess of imbibed water, which leads to the creation of a network of microscopic cracks. On the other hand, the release of the drug occurs by diffusion through a more uniformly, and less excessively swollen, polymeric matrix.

References

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